Spring 2011

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The Role of GLP-1 Agonists in Type 2 Diabetes

Improving Your Star Ratings: What You Need to Know

Effects of Medication Reconciliation on Readmissions

Magellan Rx Report

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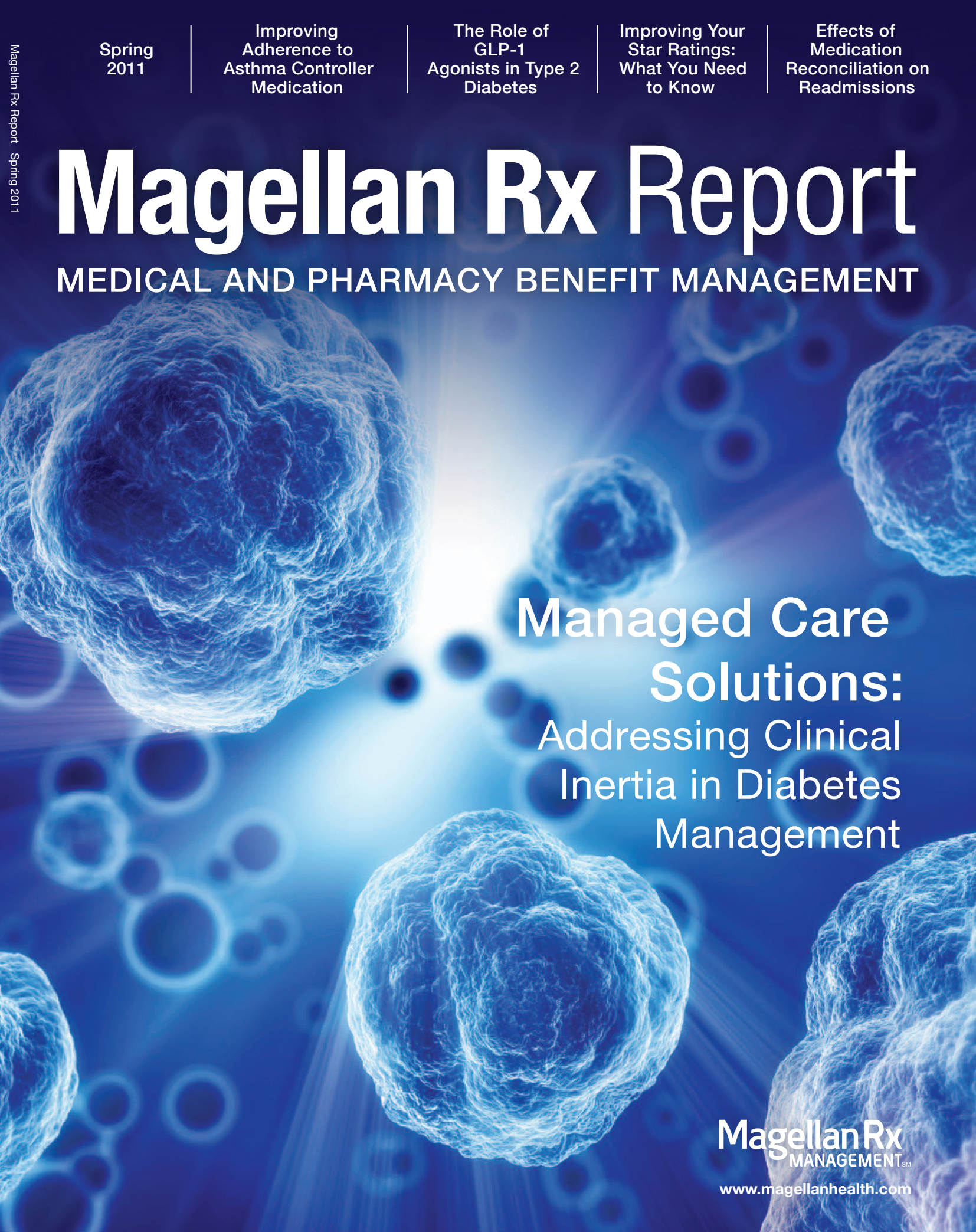

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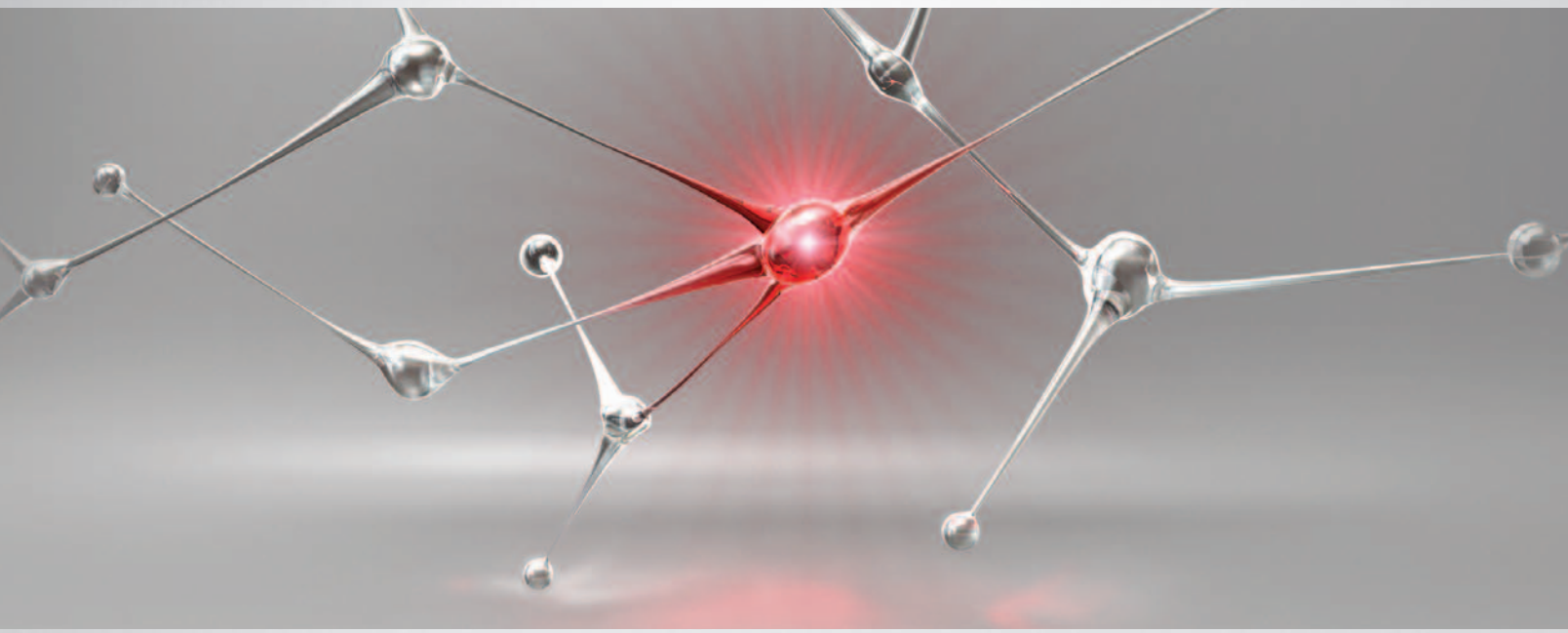

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astellas health systems

A Convergence of Innovative Therapy and Service

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CDMI REPORT

ISSN: 2159-5372

PUBLISHED BY:
CDMI, LLC
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www.CDMIhealth.com

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CDMI — Who We Are

Chronic Disease Management Solutions for Managed Care

Overview

CDMI is one of the fastest-growing chronic disease benefit management companies (CDBM) in the country, managing more than 10 million lives. We support our health plan customers in the management of chronic diseases such as diabetes, asthma, cardiovascular disease, and mental and behavioral health. Through provision of comprehensive and integrated offerings, CDMI is able to support our health plan customers with innovative solutions and services to more effectively meet their chronic disease management needs.

Susan Petrovas, RPh, President

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

Innovation and Differentiation

- Contracting and administrative support for pharmacy management programs
- Comprehensive clinical programs managed by a certified clinical team
  - Medication adherence and compliance
  - Diabetes treatment intensification
  - Asthma management: quality improvement
  - Medication reconciliation
  - Medication Therapy Management (MTM) support
  - Comprehensive medication reviews
  - Improved STAR rating support
- Development and implementation of enhanced formulary compliance support leading to significantly increased cost savings
- Appropriate utilization support, such as lowering net costs through utilization of generics or preferred brands as appropriate
- Outcomes analysis and support

With more than 35 years experience in the managed care industry, CDMI is on the fast track to becoming the premier chronic disease benefit management company in the United States.

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

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Stay on top of managed care trends and become a CDMI Report subscriber. E-mail us at **feedback@CDMIhealth.com** to subscribe today. The CDMI Report provides chronic disease management solutions for managed care executives and clinicians. We hope you enjoy the issue–thank you for reading.

ON THE COVER

This cover features a 3D rendering of particle matter and bacteria cells entering an organism.

MANAGED CARE NEWSSTAND

Heart Disease Patients May Benefit from Stress Reduction Therapy

Swedish researchers report that stress-management programs based on cognitive behavioral therapy (CBT) may lower the risk for heart attacks, strokes, and deaths in patients with heart disease. For the study, researchers compared the outcomes of patients who had standard therapy and participated in 20 two-hour stress-management sessions in one year with a control group of people who had standard therapy alone. They followed patients for nearly eight years. Those who had stress-reduction therapy suffered significantly fewer heart-related events, heart attacks, and deaths than did those in the control group.

The study suggests that long-term group interventions that incorporate techniques to change behavior may help reduce future cardiovascular events and the costs associated with them.

Source: Gulliksson M, et al. Randomized Controlled Trial of Cognitive Behavioral Therapy vs Standard Treatment to Prevent Recurrent Cardiovascular Events in Patients with Coronary Heart Disease: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). *Archives of Internal Medicine.* 2011;171(2): 134-140.

Diabetes Prevalence Rising at Alarming Rate

New estimates from the Centers for Disease Control and Prevention (CDC) demonstrate the staggering impact diabetes has on medical costs and the importance of diabetes prevention. The CDC's National Diabetes Fact Sheet for 2011 estimates that nearly 26 million Americans have diabetes. Many of them—about 7 million—do not know they have this chronic disease. About 79 million more Americans have prediabetes. The direct and indirect cost of caring for people with diabetes in 2007 was $174 billion. Medical expenses for people with diabetes were 2.3 times higher than for those without the disease.

26 MILLION
Americans have diabetes. About **7 MILLION** do not know they have this chronic disease.

Presumably, the costs of treating diabetes and diabetes-related complications will rise sharply as more people develop this disease. More aggressive interventions to control blood glucose levels can help prevent devastating and costly diabetes-related conditions.

Source: United States. Department of Health and Human Services. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011.*

Age is Not Main Cause of Health Care Usage for Seniors

A new study by researchers at the Canadian Institute for Health Information found that the number of chronic conditions seniors have—not their age—is the most significant factor affecting their use of healthcare services. Seniors with three or more chronic conditions had two times the healthcare visits as seniors in the same age group who had no chronic conditions. They also took more prescription medications and reported poorer health. Seniors taking five or more prescription medications were more likely to need medical services for side effects than those taking fewer drugs. Less than half of seniors suffering from chronic diseases had talked with their doctor about treatment plans or goals.

The study's findings regarding the prevalence of prescription side effects and the lack of communication between many patients and their physicians highlight possible areas for interventions that may lead to substantial cost savings.

Source: Canadian Institute for Health Information. *Seniors and the Health Care System: What Is the Impact of Multiple Chronic Conditions?* 2011.

New Guidelines for the Screening and Treatment of Carotid Artery Disease

New multiagency guidelines say widespread screening or routine ultrasound of the neck artery to determine stroke risk is unnecessary. The American Heart Association/American Stroke Association, the American College of Cardiology, and other groups say there is not enough evidence that general screenings for carotid artery disease are effective. The guidelines say screening is reasonable when doctors hear abnormal blood flow in the neck or patients have two or more stroke risk factors. The committee also reviewed evidence about the effectiveness of two competing methods for treating narrowed carotid arteries and restoring adequate blood flow to the brain. The guidelines say both carotid endarterectomy and carotid stenting are appropriate and effective in patients with arteries that are more than 50 percent blocked.

Source: Brott T, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation.* 2011.

Improved Medication Adherence Reduces Overall Medical Costs

CVS Caremark researchers using robust study methodologies have confirmed that improving medication adherence saves overall healthcare costs. They studied medication compliance among patients with one or more chronic vascular diseases—congestive heart failure, hypertension, diabetes, and dyslipidemia. Although enhancing compliance increased pharmacy costs, it also reduced hospitalizations and emergency room visits, resulting in significantly lower overall healthcare costs. Savings were greater in patients ages 65 and older with hypertension, diabetes, and dyslipidemia. The benefit-cost ratio—which varied by condition and age—ranged from 2:1 for adults younger than 65 with dyslipidemia to more than 13:1 for older hypertensive patients.

The researchers say their findings suggest that medication adherence programs are worth consideration if the costs of such interventions do not exceed the estimated savings.

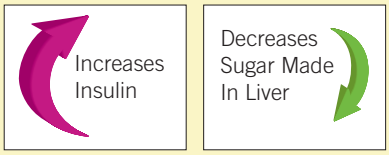
Source: Roebuck C, et al. Medication Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending. *Health Affairs*. 2011;30(1):91-99.

Cost to Treat Heart Disease Expected to Skyrocket

Medical expenses to treat Americans with heart disease will triple by 2030, according to a policy statement in *Circulation: Journal of the American Heart Association*. The American Heart Association (AHA) statement, drafted by an expert panel, attributes a significant portion of the increase to the aging population. The statement predicts that the number of Americans with heart disease will rise from 36.9 to 40.5 percent. Currently, the nation's leading killer accounts for about 17 percent of overall national health expenditures. The AHA projects that the cost of treating heart disease will increase from $273 billion to $818 billion over the next 20 years. Members of the panel who developed the statement say effective prevention strategies are needed to contain the growing burden of cardiovascular disease.

Source: Heidenreich P, et al. Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement from the American Heart Association. *Circulation.* 2011.

JANUVIA works to lower blood sugar in 2 ways. Talk to your doctor about JANUVIA today.



- **JANUVIA is a once-daily prescription pill that helps your body increase the insulin made in your pancreas and decrease the sugar made in your liver.**
- **Along with diet and exercise, JANUVIA helps lower blood sugar levels in adults with type 2 diabetes.**
- **JANUVIA is not likely to cause weight gain or low blood sugar (hypoglycemia).**

JANUVIA (jah-NEW-vee-ah) should not be used in patients with type 1 diabetes or with diabetic ketoacidosis (increased ketones in the blood or urine). If you have had pancreatitis (inflammation of the pancreas), it is not known if you have a higher chance of getting it while taking JANUVIA.

Selected Risk Information About JANUVIA: Serious side effects can happen in people who take JANUVIA, including pancreatitis, which may be severe and lead to death. Before you start taking JANUVIA, tell your doctor if you've ever had pancreatitis. Stop taking JANUVIA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

Do not take JANUVIA if you are allergic to any of its ingredients, including sitagliptin. Symptoms of serious allergic reactions to JANUVIA, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty breathing or swallowing, can occur. If you have any symptoms of a serious allergic reaction, stop taking JANUVIA and call your doctor right away.

If you take JANUVIA with another medicine that can cause low blood sugar (hypoglycemia), such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUVIA. Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heart beat, sweating, and feeling jittery.

Your doctor may do blood tests before and during treatment with JANUVIA to see how well your kidneys are working. Based on these results, your doctor may change your dose of JANUVIA. The most common side effects of JANUVIA are upper respiratory tract infection, stuffy or runny nose and sore throat, and headache.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

For a free 30-day trial supply* of JANUVIA, visit Januvia.com.

*Not all patients are eligible. Restrictions apply. See Terms and Conditions.

Please see the Medication Guide on the next page and discuss it with your doctor.

MERCK patient assistance program

Having trouble paying for your Merck medicine? Merck may be able to help. www.merck.com/merckhelps

Januvia® (sitagliptin) tablets

Medication Guide

JANUVIA® (jah-NEW-vee-ah) (sitagliptin) Tablets

Read this Medication Guide carefully before you start taking JANUVIA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JANUVIA, ask your doctor or pharmacist.

What is the most important information I should know about JANUVIA?

Serious side effects can happen in people taking JANUVIA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking JANUVIA:

Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

Stop taking JANUVIA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JANUVIA?

- JANUVIA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUVIA is not for people with type 1 diabetes.
- JANUVIA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take JANUVIA.
- It is not known if JANUVIA is safe and effective when used in children under 18 years of age.

Who should not take JANUVIA?

Do not take JANUVIA if:

- you are allergic to any of the ingredients in JANUVIA. See the end of this Medication Guide for a complete list of ingredients in JANUVIA.

  Symptoms of a serious allergic reaction to JANUVIA may include:
  - rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

What should I tell my doctor before taking JANUVIA?

Before you take JANUVIA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUVIA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.

  Pregnancy Registry: If you take JANUVIA at any time during your pregnancy, talk with your doctor about how you can join the JANUVIA pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.
- are breast-feeding or plan to breast-feed. It is not known if JANUVIA will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUVIA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take JANUVIA?

- Take JANUVIA 1 time each day exactly as your doctor tells you.
- You can take JANUVIA with or without food.
- Your doctor may do blood tests from time to time to see how well your kidneys are working. Your doctor may change your dose of JANUVIA based on the results of your blood tests.
- Your doctor may tell you to take JANUVIA along with other diabetes medicines. Low blood sugar can happen more often when JANUVIA is taken with certain other diabetes medicines. See **"What are the possible side effects of JANUVIA?"**
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JANUVIA at the same time.
- If you take too much JANUVIA, call your doctor or local Poison Control Center right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JANUVIA.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of JANUVIA?

Serious side effects have occurred in people taking JANUVIA.

- See **"What is the most important information I should know about JANUVIA?"**
- **Low blood sugar (hypoglycemia).** If you take JANUVIA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUVIA. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heart beat
  - sweating
  - feeling jittery
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUVIA and call your doctor right away. See **"Who should not take JANUVIA?"**. Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

The most common side effects of JANUVIA include:

- upper respiratory infection
- stuffy or runny nose and sore throat
- headache

JANUVIA may have other side effects, including:

- stomach upset and diarrhea
- swelling of the hands or legs, when JANUVIA is used with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.

These are not all the possible side effects of JANUVIA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JANUVIA?

Store JANUVIA at 68°F to 77°F (20°C to 25°C).

Keep JANUVIA and all medicines out of the reach of children.

General information about the use of JANUVIA

Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JANUVIA for a condition for which it was not prescribed. Do not give JANUVIA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JANUVIA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUVIA that is written for health professionals. For more information, go to www.JANUVIA.com or call 1-800-622-4477.

What are the ingredients in JANUVIA?

Active ingredient: sitagliptin.

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. The tablet film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Insulin Therapy and Clinical Inertia:
The Costs for Patients and Health Systems

Jeremy Gleeson, MD, FACP, FACE, CDE, Endocrinologist, Associate Medical Director, ABQ Health Partners, and
Debra Gordon, MS

Type 2 diabetes is a chronic, progressive metabolic disorder associated with obesity and physical inactivity.[1] Currently, 10.6 percent of people ages 20 and older in the United States have diabetes, but a recent report from the Centers for Disease Control and Prevention (CDC) predicted that by 2050, up to 1 in 3 Americans would have diabetes, most of them type 2.[2,3] As the authors of that study wrote, this is a "sobering picture of the future growth of diabetes." Even a best-case scenario showed 1 in 5 Americans with the disease, a prevalence "significantly worse" than the 1 in 10 Americans previously suggested. Given the staggeringly high costs of diabetes—more than $174 billion in 2007—and its high morbidity and mortality rates, these projections are, quite simply, frightening.[4]

Currently, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend that patients with Type 2 Diabetes Mellitus (T2DM) be treated with a combination of lifestyle changes and medications, including early initiation of insulin therapy, to attain and maintain an HbA_{1c} of <7 percent.[1] The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend treating to an HbA_{1C} of ≤6.5 percent, using as many as three oral and/or injectable drugs before moving to insulin.[5] Unfortunately, there are no well-controlled randomized trials that rigorously establish which approach, if any, is preferable.

Although the professional societies have tried to develop guidelines and treatment algorithms that are as simple as possible, and while all are based on extensive clinical evidence, it is clear that patients in the United States and elsewhere with T2DM often do not receive guideline-recommended care.

Although glycemic levels in people with diabetes living in the United States have improved slightly since 1999, they are far from ideal. An analysis of data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) found that mean HbA_{1C} levels were 7.18 percent, which is significantly higher than recommended levels.[6] A more recent study using data from the 2005-2006 NHANES found that even as the prevalence of diabetes (Type 1 Diabetes Mellitus [T1DM] and T2DM) significantly increased, just 57.1 percent of patients achieved glycemic goals.[7]

Jeremy Gleeson, MD

Thus, as the AACE noted in its 2007 guidelines for diabetes management, "Clearly, earlier and more aggressive application of available treatments and technologies is needed."[8]

Part of that aggressive approach to diabetes management involves initiating insulin therapy early. It is clear that early and maintained management of glucose levels can reduce the risk for microvascular and neuropathic complications in patients with T2DM. Additionally, when initiated early in the disease state, glucose control may have some benefit in preventing macrovascular complications.[1,9-12]

Patients who switched to insulin therapy from oral therapy, or for whom insulin is added to oral therapy, demonstrate significant improvements in quality of life and fewer physical complaints than prior to insulin initiation, primarily because of improvements in metabolic control.[13, 14]

There is also evidence that initiating insulin immediately upon diagnosis significantly improves glycemic control. In other words, the traditional step-based management algorithm increases the risk of complications in patients with T2DM.[15] When low doses of insulin are added to sulfonylurea therapy before such therapy fails completely, the combination can maintain lower HbA_{1C} levels than insulin alone and lead to more patients reaching target with no increased risk of weight gain or major hypoglycemia.[16]

Numerous studies also suggest that a short course of insulin therapy upon diagnosis may induce remission for up to two years in some patients while improving long-term glycemic control in others.[17-22]

There are also nonglycemic benefits to insulin therapy, including reduced inflammation and possible antiatherogenic effects that may potentially decrease morbidity and mortality following cardiovascular events.[23] This has not been definitively established, however.

Yet whether in the short term or long term, primary care physicians in this country wait too long to start their patients on insulin, contributing to an increased risk for complications as well as increased economic costs.[24] They tend to believe that insulin therapy should be delayed as long as possible.

The reason is clinical inertia.

Clinical Inertia Defined

Clinical inertia occurs when clinicians do not initiate or intensify therapy appropriately, even when the goals for managing a particular condition are well defined, effective therapies are widely available, and practice guidelines for each of these diseases has been disseminated extensively.[25] As Phillips et al noted in their 2005 seminal article on the topic, clinical inertia is "recognition of the problem, but failure to act."

Phillips et al suggest that clinical inertia is a problem of the healthcare professional and the healthcare system, and is unrelated to issues of patient access and adherence. It is not related to a lack of knowledge on the part of physicians, at least when it comes to diabetes. They suggest that clinical inertia results from overestimating the quality of care the physicians provide; the perception that the disease is controlled or that patient nonadherence is the reason for the lack of control; and a lack of education and training on implementing evidence-based medicine in daily practice. They also note that physicians have little education in treating to target. There may be a willingness to defer pharmacologic intervention based on the patient's stated intent to improve adherence to diet or exercise. Unfortunately this continues indefinitely as promised improvements never come to fruition.

There is significant evidence for clinical inertia in diabetes, particularly in the primary care setting, where most diabetes is managed. Among the evidence:

- When researchers evaluated clinical decision making over three years in a hospital-based diabetes clinic in Atlanta, they found that therapy was intensified just 36 percent of the time in patients for whom more intensive therapy was justified.[26]
- Ziemer et al compared glycemic control in patients attending a specialized diabetes clinic versus a primary care clinic, settings in which clinicians at both clinics had access to exactly the same medications: sulfonylureas, metformin, and insulin. Regardless of the type of therapy used, patients

7.18%

An analysis of data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) found that mean HbA_{1C} levels were 7.18 percent, which is significantly higher than recommended levels.

in the primary care clinic had higher glycemic levels. A major factor in the glycemic control difference was that fewer patients in the primary care clinic were receiving insulin.[27]

Physicians in the primary care clinic were significantly less likely to intensify therapy when random glucose levels were greater than 50 mg/dL above target (32 vs. 65 percent, P<0.0001), regardless of which therapy the patient was receiving. Of particular note is that patients already using insulin had their therapy intensified just 28 percent of the time, compared with 75 percent of the time for those seen in the specialty clinic.[28] Yet physicians who were more willing to intensify their patients' therapy had patients with lower HbA_{1C} levels (P<0.0001). A single episode of therapy intensification was associated with an average 0.7 percent reduction in HbA_{1C} levels.

"Overcoming clinical inertia is not likely to be easy, but it is essential if we are to substantially improve health outcomes for patients with diabetes." *—Berlowitz et al*

■ Berlowitz et al evaluated glycemic status and medications in 23,291 patients with diabetes in 13 Department of Veterans Affairs hospitals between 1997 and 1999. They found patient therapy was intensified just 9.8 percent of the time, despite the fact that 39 percent of patients had HbA_{1C} levels >8 percent. Even after an average of 11 visits per patient over 16 months of care, glycemic control among patients remained virtually unchanged. Yet, as expected, patients who received therapy intensification had the greatest improvement in control.[29]

The need to intensify therapy in patients with diabetes and uncontrolled HbA_{1C} levels is simple: If the HbA_{1C} level, a marker of glycemic control over several months, is not at goal, therapy should be changed. As Berlowitz et al noted: " ... Overcoming clinical inertia is not likely to be easy, but it is essential if we are to substantially improve health outcomes for patients with diabetes."

Barriers to Insulin Initiation

There are numerous barriers to insulin initiation on both the patient and physician sides. Patients may worry that they won't be able to manage insulin therapy on their own and fear the pain of injections and the potential for hypoglycemia. They may view their need for insulin as a personal failure; this is made worse when physicians "threaten" patients with having to use insulin if they don't eat right, exercise, lose weight, and take their oral medications. To some patients, moving to insulin suggests their disease has become much more serious, even if they don't feel any worse. Some patients worry that the insulin itself will make their disease worse, often because they saw the disease worsen in friends or relatives after beginning insulin. They don't understand the natural progression of T2DM, and attribute the adverse outcomes to the insulin treatment rather than the disease itself.[30, 31]

However, physicians have their own barriers to initiating insulin therapy. These include the time required to educate patients; a lack of confidence in clinician ability to properly dose insulin; concerns about unpleasant confrontations with patients; and beliefs that the patient is not competent to manage insulin properly. Providers also worry about hypoglycemia and weight gain and doubt that there are beneficial outcomes to insulin therapy in T2DM.[23] In fact, in one study only just over half of physicians and nurses agreed that insulin could have a positive impact on care.[24] There is also evidence that patient nonadherence contributes to clinical inertia; if physicians think that their patients won't use the medication as directed, they are less likely to prescribe it.[32]

In one survey of 505 primary care physicians, 80 percent thought their patients were afraid of insulin therapy, 72 percent said their patients would probably not accept a prescription for insulin therapy, and 66 percent said initiating insulin therapy was one of the most difficult areas of diabetes management.[33] Interestingly, the physicians said that the benefits of insulin therapy outweighed the risks and improved their patients' well-being.

In an interesting survey of 850 primary care physicians and diabetes specialists, the specialists reported no patient-related barriers to insulin initiation, whereas the primary care physicians said patient fears about insulin injections and their desire to give lifestyle changes and oral medications more time to work were major barriers.[32]

Overcoming Clinical Inertia

It is possible to overcome clinical inertia. First, highlighting the benefits of today's newer insulins, including simpler dosing algorithms, reduced risk of hypoglycemia and weight gain, and nearly painless delivery devices such as pens, is essential.[34-36] If primary care clinicians understand that these newer regimens can reduce the time required to educate patients and manage potential problems, they may be more willing to discuss the options with their patients. This is important, since the attitude of the physician directly impacts patient attitudes about therapy.[37,38]

It is also important to address physician misconceptions about insulin therapy. Among 550 primary care physicians in the United States surveyed about initiating insulin therapy in their patients, 40 percent said their patients wouldn't need insulin if they were more adherent to treatment recommendations, and a third thought that increased plasma insulin levels would increase cardiovascular risk.[33]

Practice-based interventions such as electronic or paper reminders to regularly check HbA_{1C} levels, flow charts, and face-to-face academic detailing have all demonstrated improved adherence to guideline-recommended care.[28, 39-42]

Ziemer et al found that internal medicine residents who received personalized feedback on their performance every two weeks with or without computerized reminders on patient-specific recommendations were more likely to intensify therapy in patients with diabetes than a control group ($P<0.001$). After three years, physicians who had received personalized feedback with or without computerized reminders demonstrated sustained improvement compared with control and the computerized reminder group only ($P<0.001$).[28]

Conclusion

As the obesity epidemic continues to grow in the United States, it is imperative from a public health and medical economics perspective that, if diabetes cannot be prevented, it be managed as well as possible to reduce the risk for complications.

Knowing when patients should begin insulin therapy is an important component of appropriate management, and one in which there is significant room for improvement in the primary care setting. Managed care organizations, by virtue of their focus on quality as well as cost, are in an optimal position to institute evidence-based interventions designed to improve glycemic control in their members with diabetes.

Current Guidelines for Glycemic Control in Patients with Type 2 Diabetes

- Perform the HbA_{1C} test at least two times a year in patients who meet treatment goals and have stable glycemic control and quarterly in patients who are not meeting glycemic goals.
- The goal to prevent microvascular complications is an HbA_{1C} <7 percent for most patients.
- Intervene at time of diagnosis with metformin and lifestyle changes.
- Continue augmenting therapy with additional agents, including early initiation of insulin therapy, to achieve and maintain recommended levels of glycemic control (HbA_{1C} <7 percent).

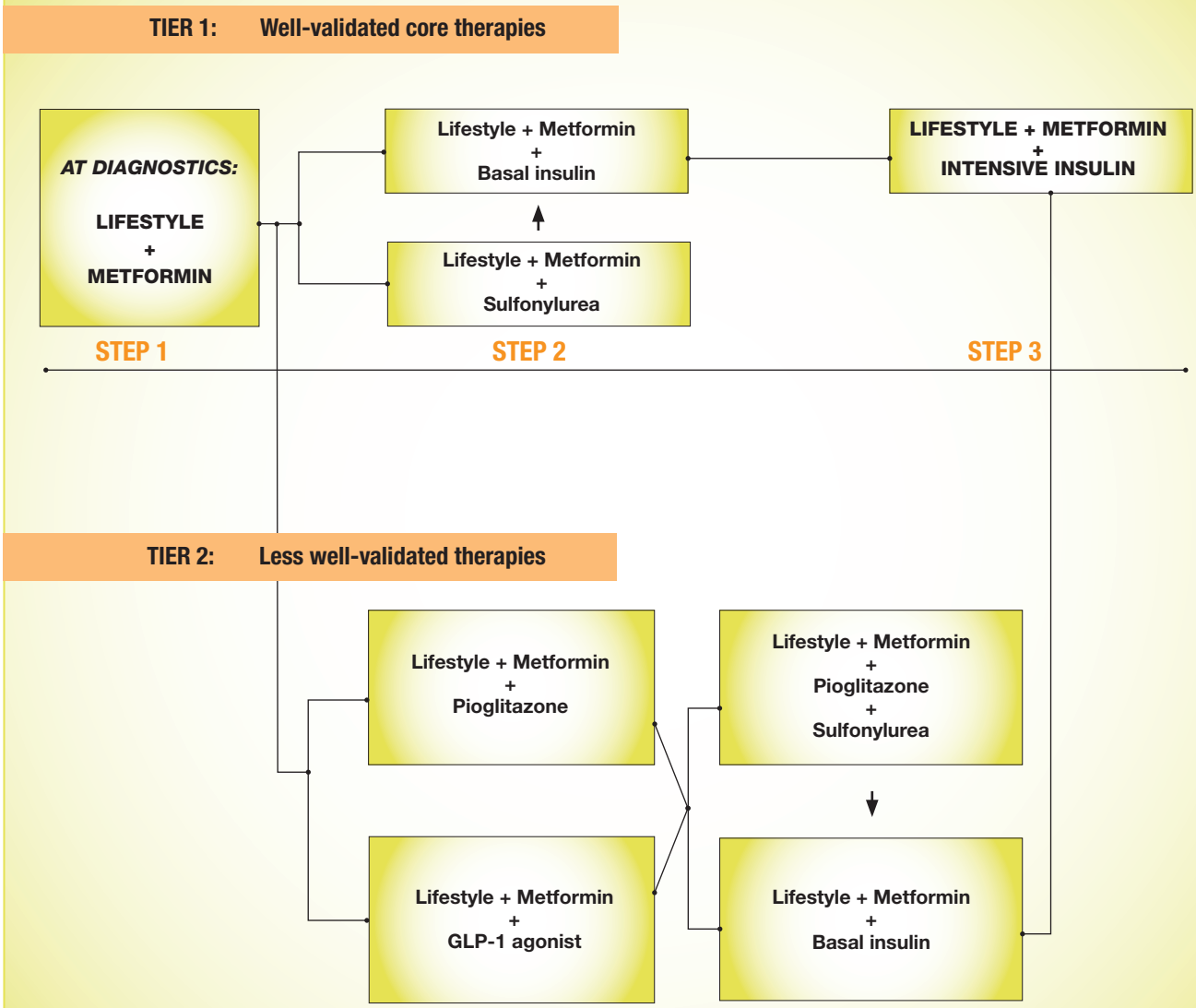
American Diabetes Association[1]

AACE/ACE Consensus Statement on the Treatment of Type 2 Diabetes Mellitus

- Achieve HbA_{1C} of 6.5 percent as primary goal, but customize according to individual patient considerations.
- Evaluate effectiveness of therapy every two to three months, including assessing HbA_{1C}.
- Rapid-acting insulin analogues are superior to regular human insulin and provide a better, safer alternative.
- Neutral protamine hagedorn (NPH) insulin is not recommended.
- Stratify therapy by HbA_{1C} level:
  - HbA_{1C} ≤7.5 percent, monotherapy may be sufficient.
  - HbA_{1C} 7.6 to 9 percent, dual therapy required.
  - HbA_{1C} >9 percent, triple therapy may be used in asymptomatic patients; initiate insulin therapy with or without oral agents in patients who are symptomatic or failed triple therapy.

American Association of Clinical Endocrinologists/ American College of Endocrinology[8]

Fig. 1 ADA AND EASD CONSENSUS ALGORITHM FOR INITIATION AND ADJUSTMENT OF THERAPY IN T2DM[43]



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How Health Reform May Change the Business Landscape of Health Care

Todd C. Lord, PharmD, Manager of Compliance and Adherence Programs, CDMI

The saga of U.S. health reform may have seemed never-ending as it proceeded through 2009, with the signing of the Patient Protection and Affordable Care Act of 2010 (PPACA) and its companion Health Care and Education Reconciliation Act of 2010. However, PPACA is now the law of the land. The far-reaching bill introduced a number of changes in the U.S. healthcare system that will have profound effects on insurers and providers over the next several years. Among the most significant changes are:

- **New essential benefits requirements**: Beginning in 2010, the PPACA mandates that insurers cover a minimum set of "essential" health benefits, to be determined by the Secretary of Health and Human Services, and links those benefits to cost-sharing limits.
- **Medical loss ratio (MLR) provisions:** Starting in 2011, PPACA requires insurers to verify that a percentage of all premiums (85 percent in large group markets; 80 percent in small group and individual markets) is spent on direct clinical care or other programs that directly affect the quality of care. Insurers are required to report annually on their compliance with this requirement.
- **Establishment of exchanges:** States are required to set up health insurance exchanges by 2014 to serve as marketplaces for individuals and small businesses to shop for and purchase insurance.
- **Expansion of the 340B drug pricing program:** Historically, the 340B program required drug manufacturers to provide deep discounts of 30 to 50 percent to qualified hospitals and community health centers serving significant indigent populations. Under PPACA, this program is being expanded as of January 2010 to many more types of hospitals, including rural hospitals, children's hospitals, cancer centers, and others.
- **Establishment of Accountable Care Organizations (ACOs):** In an effort to help control Medicare spending, PPACA requires the Centers for Medicare and Medicaid Services (CMS) to create ACOs by January 2012. As loosely proposed in the bill, ACOs would more tightly coordinate care for Medicare patients among the various types of providers (hospitals, specialists, home health, etc.) and compensate them as a group, based on meeting outcome and quality targets, rather than on a fee-for-service basis.

Todd C. Lord, PharmD

While there is broad agreement in the industry regarding the scale of change that PPACA represents, insurers and providers do not yet know what these reforms will specifically mean for their businesses. In particular, the degree to which PPACA reforms will affect reimbursements to providers is still unclear. CDMI asked industry experts from various managed care organizations to provide their insights into these questions.

CDMI Report: In the broadest sense, how do you anticipate the health reform bill affecting provider reimbursements?

MC Executives: The simple answer is that we just don't know yet. This is a 2,000-page piece of legislation that is extremely nuanced and will drive a wide range of changes that we cannot yet predict. Ultimately, we will have to wait and see what happens in the marketplace and in Washington. However, based on the specifics we do know, we can make some educated guesses.

For insurers, the most significant likely impact of healthcare reform is that they will have no choice but to seek to control costs. Unfortunately, one of the primary ways to control cost is to control reimbursements. Whether in the end that means direct reductions in the fee schedule or a more concerted effort to collaborate with providers to align goals and control costs remains to be seen.

CDMI Report: What aspects of health reform have the greatest influence on cost concerns?

MC Executives: We know that there are essential benefits that will be required for coverage by any healthcare insurer. These are services that, if we do cover them today, typically require a member share contribution of some sort. Under the new law, these services must be provided with basically zero liability from the member. In addition, we have the new medical loss ratio regulations that went into effect in January 2011. It remains to be seen how well insurers or payers can realistically cope with these medical loss ratios that have been put in place.

Together, these reforms create a two-pronged challenge that insurers suddenly have to contend with. On the one hand, we are required to provide expanded coverage for low-income members at a reduced premium. At the same time, in order for these new members to participate, they will be signing up for these plans through the new state insurance exchanges that people are now frantically trying to put together.

Obviously, insurers will need to find ways to compete effectively on these exchanges. If prospective members are allowed to virtually shop around on an exchange, rates will have to be very competitive. So how will insurers compete? Once again, they will need to find ways to control costs, whether that is achieved through lower reimbursements or by working collaboratively and creatively with providers.

CDMI Report: What should insurers be doing now while waiting for these questions to be sorted out?

MC Executives: As a group, insurers have implemented those programs they've been required to implement, [as well as] the medical loss ratio reporting and essential benefits requirements that went into effect last October. And as expected, their costs are going up as a result. Beyond that, though, most insurers are just waiting to see what will happen. There is just too much uncertainty right now, especially politically. We could spend enormous amounts of time and resources trying to figure out how various aspects of the reform bill need to be implemented, only to see that provision eliminated at the 11th hour because of changes in Congress.

So for most insurers, the thrust of what we're doing today is still what our bread and butter always has been. We are trying

2014

Deadline by which states are required to set up health insurance exhanges.

to control costs and working to improve collaboration with physicians, so that we can get the best outcomes for our members and the best value for what we're paying.

CDMI Report: What will changes to the federal 340B drug pricing program mean for insurers and providers?

MC Executives: We think it will be very interesting to see how these changes play out. From the insurer's perspective, if more hospitals are able to get medications at a deeply discounted price, the insurer ought to be able to lower reimbursement schedules for those drugs accordingly. Naturally, insurers don't see why they should maintain a higher cost for these drugs than providers, just to create a better margin for hospitals. And yet, while this proposition seems fairly straightforward, it remains to be seen how insurers and providers will hash this issue out. Because just as insurers are looking for ways to cut expenses to operate in this new climate, providers are frantically searching for new resources as well.

We believe that the patient-centered medical home model will provide patients with the best care, sustain providers, and give insurers the best bang for their buck.

For example, the reform bill introduces this concept of ACOs. Despite the fact that no one is quite sure yet what an ACO actually looks like, the idea is generating an enormous amount of buzz in the industry. Hospitals are out making new alliances with independent physician practices, and in many cases, looking to literally buy the practice with the goal of controlling utilization, so that they can be among the first to bring an ACO to fruition.

Of course, this kind of business expansion requires resources. If hospitals are going out and investing in alliances with all these new physician practices, they need to be making a profit somewhere else. And in fact, many providers are looking at these changes to the 340B program as precisely the solution to finance these ACO alliances. So from the hospital's perspective, if insurers now reduce reimbursements in response to the 340B changes, those margins are erased. The hospitals no longer have the funds to aggressively go out and create ACOs. Potentially, you are looking at a total breakdown of the system.

CDMI Report: So what can be done to resolve this discrepancy?

MC Executives: The key, we believe, and which we think most insurers and providers are looking to accomplish, is to move toward the primary care, patient-centered medical home model. Even within the context of ACOs, we don't believe the ACO model can survive without a primary care and medical home underlying it. If you imagine the ACO as the roof covering the entire healthcare structure, the primary care medical home model would be the walls holding that roof up.

We don't believe the ACOs within themselves can control utilization and monitor the patients with the best outcomes. It really has to come down to the grassroots physician level. As insurers, that's where we're concentrating our efforts today: trying to provide more tools and information to help a primary care physician coordinate the overall care of the patient. Ideally, we would like to see a much more collaborative effort toward that model than what we have had in the past. We believe that the patient-centered medical home model will provide patients with the best care, sustain providers, and give insurers the best bang for their buck.

Looking Ahead

The details of all the changes likely to occur as a result of healthcare reform may still be unknown, but insurers and providers are carefully watching these developments as they unfold. Regardless of how the landscape of healthcare changes, however, one thing seems clear: To sustain an operable business model and maintain a high quality of care, insurers and providers will need to collaborate more closely than ever before. Whatever else may change in the coming months and years, insurers and providers should be looking to develop the tools and initiatives to enable that collaboration right now.

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- Medication Therapy Management (MTM) support
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- HEDIS measure and Star Rating improvement support
- Medication reconciliation and comprehensive medication reviews
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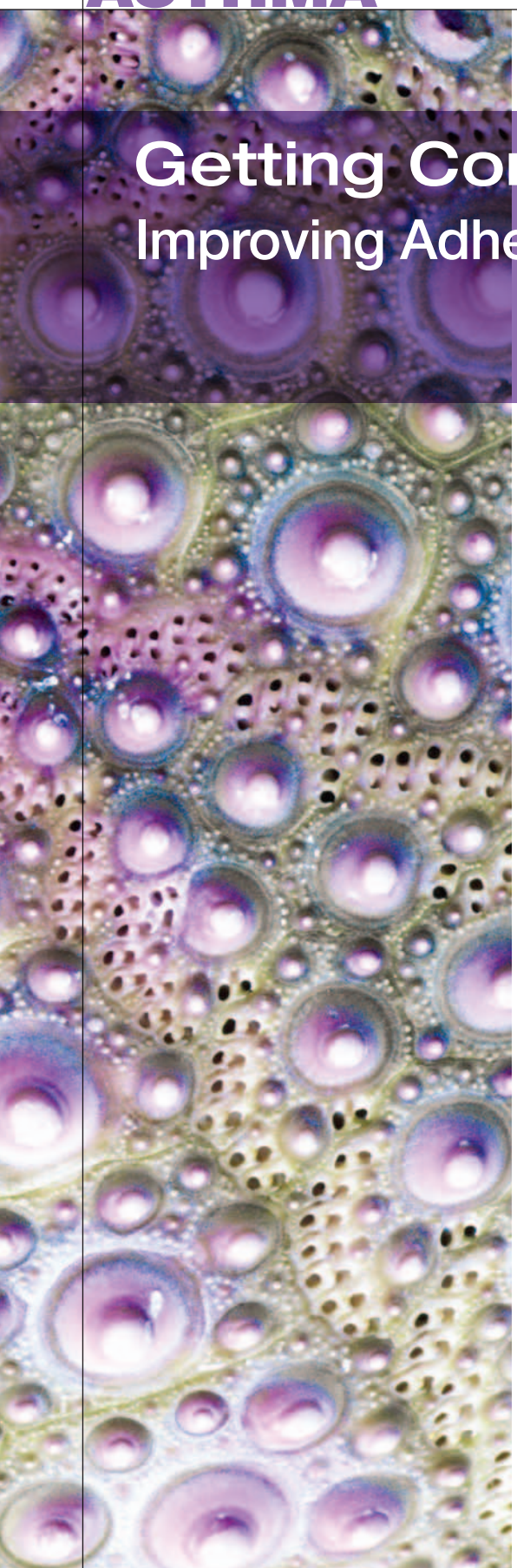

Getting Control of Asthma:
Improving Adherence to Controller Medication

John Fox, MD, Senior Medical Director, Priority Health;
Steve Cutts, PharmD, AE-C, Manager of Clinical and Compliance Programs, CDMI; and
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Despite advances in diagnosis and pharmacotherapy, asthma remains a cause of substantial morbidity and imposes a significant burden on the healthcare system. Asthma affects more than 22 million Americans, including 6 million children, and leads to 440,000 hospitalizations, 10.6 million physician visits, and 1.7 million emergency department visits each year.[1, 2] Annual medical costs are estimated to be $15.6 billion,[3] making asthma one of the most costly chronic diseases. Physician office visits and prescription medications account for 49 and 38 percent of these costs, respectively.[4]

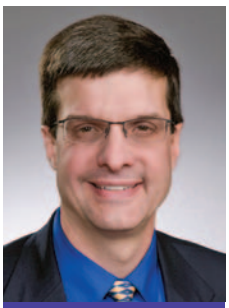
Inability of patients to adhere to treatment contributes significantly to asthma costs.[5,6] A 25 percent decrease in asthma controller medication refills has been linked to a doubling of the rate of asthma-related hospitalization.[7] Various studies show that only 20 to 50 percent of asthma patients routinely use controller medication as prescribed.[8] A systematic review of studies reported that patients underused prescribed inhaled corticosteroids (ICS) on 24 to 69 percent of days.[9]

Although medication nonadherence is pervasive, it is most likely to occur in persons with severe asthma, in part because of their more complex medication needs.[6, 10] The medical costs of severe asthmatics are more than four times higher than those of mild asthmatics.[11] To improve asthma control, it is important to understand and address common barriers to the daily use of controller medication, particularly ICS, which are considered the most effective treatment for persistent asthma.[12]

Barriers to Controller Medication Adherence

The causes of nonadherence are complex, and addressing the problem requires a multifaceted approach. The treatment regimen itself, as well as patient, provider, and organizational factors, can be involved.[6]

Treatment-related barriers to adherence include prescription copayments and other out-of-pocket drug costs borne by the patient.[10] The complexity of the patient's drug regimen, including the number of medications and dosing frequency, is also a factor.[10, 12] The long-term nature of controller medication effects is an additional obstacle.[10] The benefits of ICS lie in the prevention of symptoms and exacerbations, effects the patient may not perceive in the short term.[6, 10] Patients are far more likely to comply with treatments that provide immediate relief of symptoms.[10] Nonadherence also can occur because patients forget to refill prescriptions, forget to take a dose, or misplace their medication. They may skip doses due to



John Fox, MD

Steve Cutts, PharmD, AE-C

concern about side effects—whether valid or not—or because they don't understand how the medication works or don't believe it benefits them.[6, 13] Even when intentions are good, many patients have such poor technique when using an inhaler that the full dose of medication doesn't reach the distal alveoli and bronchioles in the lungs.[1]

There are also provider- and organizational-specific factors that contribute to medication nonadherence. Physicians may not be aware that current practice guidelines recommend daily controller medication for persistent asthma, or they may prescribe rescue medication alone due to concerns about ICS side effects.[14] Continuity of care can suffer when the patient is treated by more than one provider, has difficulty scheduling appointments,[10] or receives frequent care in urgent care or emergency department settings. Add the time constraints of the typical outpatient visit, which make it difficult for providers to adequately educate patients or monitor inhaler technique, and the high rates of nonadherence are not surprising.

Strategies for Improving Adherence

There is substantial evidence that improving controller medication adherence can reduce asthma-related hospitalizations and emergency department visits and improve patient quality of life.[6, 10] The following interventions have the potential to improve adherence.

Patient interventions: Intensive, patient-centered educational efforts are a vital means to improve adherence and outcomes, yet asthma education has declined in recent years. Education was provided in only 38 percent of asthma-related primary care visits between 2005 and 2006, compared with 50 percent of visits between 2001 and 2002.[15,3] The National Asthma Education and Prevention Program (NAEPP) recommends that patient education begin at diagnosis, continue through follow-up, and be provided at every contact with a health professional, including in the clinic, office, hospital, emergency department, and pharmacy settings.[16] Various educational models have resulted in increased ICS use, decreased emergency department use and hospitalizations, and fewer missed days and sick days. The most effective approaches provide skills-training; tailor self-management education to the individual; emphasize use of written asthma action plans; and involve patients in decision-making.[16] Both group and one-on-one teaching formats are often used.[16, 17] In a study in an outpatient specialty care setting, children in the intervention group attended one educational session with a physician who discussed behavioral strategies and provided written drug information. Their subsequent medication compliance was significantly better than that of the control group (78 percent versus 54.5 percent).[1]

Physicians generally face time constraints during a usual office visit, and may lack expertise and confidence in providing tailored interventions for their patients, particularly if asthma is not the provider's specialty. An additional hurdle is that many healthcare providers may be unaware that asthma education is reimbursable. Medicare and Medicaid reimburse for services provided by Certified Asthma Educators (AE-C),[18] who are nurses, pharmacists, physicians, or other healthcare providers with extensive, specialized training in the provision of asthma education. They are thus well-positioned to deliver comprehensive asthma education that might be otherwise impossible for a physician to convey during a usual office visit. However, there are only about 3,100 AE-C nationally,[19] compared to 24 million Americans living with asthma. To overcome this discrepancy at the local level, health plans may find it advantageous to sponsor certification programs or promote certification by enhancing the rates for asthma education services.

Brief, patient-specific interventions also can improve adherence. Telephone follow-up between outpatient visits and reminder letters can be used to monitor progress and reinforce adherence to controller medication.[8] At the Kaiser Permanente Northwest managed care organization, an automated voice-recognition telephone system was used to offer support and information, as well as flag patients with poor control for follow-up by a provider.[20] The intervention was associated with greater use of ICS, less use of rescue medication (short-acting beta-agonists, [SABA]), and improved asthma-specific quality of life. In a small randomized clinical trial of 50 adults, a telephone intervention similar to that

used at Kaiser resulted in a 32 percent higher ICS adherence rate.[21] Patients who reported they had experienced asthma symptoms in the week prior were reminded that their controller medication could prevent symptoms and were given the opportunity to learn the difference between rescue and controller medication.

Text messaging reminder systems have also gained popularity in recent years, likely due to their relative ease-of-use and minimal resource investment. Though promising, results have been mixed; many studies have shown improvements in medication adherence and symptom scores, but data on the long-term effectiveness of the interventions is lacking.[22,23] In addition, the generalizability of many studies is limited by their small sample sizes and lack of geographical variation. However, they may prove intriguing to health plans that seek to implement scalable initiatives that present potential benefits without requiring the investment of substantial resources.

Provider education interventions must not only reinforce guideline-based asthma care, but build skills for communicating with asthma patients and their caregivers.

More extensive telephonic interventions also have been successful. In 2001, ConnectiCare Inc. & Affiliates regional managed care organization incorporated the Asthma Treatment Awareness Project into their existing asthma management program. For a six-month period, nurse case managers provided monthly telephonic self-management educational sessions and individualized packets of educational materials to members enrolled in the program. During the 12-months encompassing the intervention and follow-up periods, there were significant increases in the utilization of controller versus rescue medications, with a nearly twofold increase observed for the intervention group as compared with the control group.[24]

Despite evidence indicating beneficial effects of telephone- and other distance-based interventions in the treatment of asthma, there is lack of consensus as to the overall benefits of its use. A Cochrane Review analyzed 21 randomized controlled trials employing a variety of technologies used to deliver asthma-related interventions from a distance and found that they are unlikely to improve quality of life in those patients with mild asthma.[25] The reviewers note, however, that such telehealthcare initiatives might be useful in managing those with more severe asthma. Thus, managed care organizations looking to improve the quality of care for their asthma patients through distance-based activities should develop and implement such programs in the context of their available resources and anticipated target populations.

Provider interventions: Physicians may have a tendency to underestimate their patients' asthma symptoms and overestimate their level of asthma control,[13] and poor communication between provider and patient is part of the problem. A 2007 study examined the perceptions of medication-related communication between 96 providers practicing across six states and 1,100 of their patients. Among other noteworthy considerations, it was found that "eighty-three percent of patients would never tell their physician if they did not intend to fill a prescription, and physicians seemed oblivious to the extent to which this lack of communication exists." Discord was also found between patient and provider reports of the frequency with which discussions pertaining to adverse effects of medications, costs of therapy, and medication use occur.[26] Thus, provider education interventions must not only reinforce guideline-based asthma care, but build skills for communicating with asthma patients and their caregivers.[16]

Providing literature, targeted one-to-one academic detailing, and other forms of clinical decision support can further assist providers in prescribing those controller medications and simplified drug regimens that are most likely to benefit the patient and foster medication adherence.[27, 28] Insertion of an asthma care section within the medical chart is a fairly simple but useful intervention. The section can include a protocol for managing asthma exacerbations and reminders to review treatment guidelines and formally determine the patient's asthma control status using the Asthma Control Test or another validated instrument.[1]

The above measures could be particularly effective when used in tandem with patient asthma action plans (AAP), which are considered cornerstones of asthma management. They include instructions for the daily management of asthma, such as proper use of medications and management of environmental factors, as well as how to recognize and address signals that an exacerbation may be occurring.[16] A recent systematic review examined the relationship between the use of asthma action plans and asthma exacerbations in children with asthma. In five out of eight studies comparing use of AAP with no AAP, there

were significant decreases in absenteeism, nocturnal awakenings, restricted activity, acute episodes, hospitalizations, and emergent care utilization.[29] A Cochrane Review examining the results of trials that compared asthma self-management education to usual care found that "asthma sufferers who were educated about their asthma, visited the doctor regularly and who used a written action plan had fewer visits to the emergency room; less hospital admissions; better lung function; improvement in peak expiratory flow; fewer symptoms; and used less rescue medication."[30] Evidence is conflicting as to whether a symptom- or peak-flow-based AAP is more effective,[29, 31] but it is clear that use of AAP is vital to asthma management. As such, the EPR-3 and other guidelines, such as the Global Initiative for Asthma (GINA), recommend that they be provided to all patients with asthma.[16, 32] These efforts can be supported by health plans through regular outreach to ensure the providers in their coverage network both possess and utilize the necessary resources to appropriately manage their patients with asthma.

Automatic or user-initiated computerized physician order entry programs are increasingly being used. They have been most consistently effective in fine-tuning existing pharmacologic therapy in terms of dose, duration, and safety.[28] In a Michigan health plan, ICS adherence was 35.7 percent among patients of providers who viewed their detailed ICS adherence data via an electronic prescribing system, but only 12.3 percent among patients whose providers chose not to view this information.[33] This suggests that no asthma management tool will be effective if providers are not motivated to use it, and also indicates that there is substantial potential for improvement when providers desire to improve quality of care for their patients.

The report "Closing the Quality Gap—A Critical Analysis of Quality Improvement Strategies" (Agency for Healthcare Research and Quality, 2007) examined available data and found that although results are mixed, provider education programs can lead to significant improvements in asthma care, including increased prescribing of inhaled controller medications.[1] Distributing guidelines alone does not result in improved care, however.[16, 27] Multifaceted, peer-led education and interactive teaching methods are most likely to lead to improved care practices and positive patient outcomes. The most effective approaches use interactive learning strategies and are implemented along with multifaceted, tailored interventions.[16]

Patient and provider incentives: A more recent approach to improving adherence is offering copayment waivers and discounts on insurance premiums or deductibles to patients who show continued, regular use of controller medication.

37%

A recent analysis of claims data found that patients adhered to ICS therapy only 37 percent of the time.

Providers may also respond to incentives. One successful asthma education program offered free continuing medical education, a malpractice insurance discount, and free patient education materials as incentives for providers to participate in workshops.[12, 23] Although only 33 percent of targeted providers participated in the intervention, Medicaid claims for emergency care of asthma dropped by 41 percent among the patients of those providers who did participate.[16, 34] Other arrangements, such as pay-for-performance programs (P4P) commonly employed by HMOs, have been used as a means to incentivize providers to deliver high-quality, evidence-based asthma care, with varying results. There is evidence to suggest that implementing structural features of a P4P program in parallel with more intensive quality improvement initiatives, such as use of multidisciplinary management teams and web-based asthma registries, can improve use of controller medication, asthma action plans, and seasonal flu vaccination rates.[35]

The new healthcare reform legislation will likely cause an even greater shift toward provision of incentives for quality care. The creation of Accountable Care Organizations (ACOs) is a vital piece of the Patient Protection and Affordable Care Act (PPACA) that builds upon the concepts of the Patient-Centered Medical Home (PCMH) to foster accountability for quality patient care across the care continuum. The realization of shared savings payments for providers, received as a result of meeting or exceeding quality thresholds for patient care, are powerful incentives for provider cooperation and coordination of patient services throughout all phases of treatment.

Monitoring claims data: Pharmacy data can be used to identify individuals who do not obtain adequate fills of controller medication or who overuse rescue medication, an indication of poor asthma control,[36] and possible provider nonadherence to asthma treatment guidelines. Once patients are identified, targeted interventions can be implemented, such as physician alerts and patient outreach calls and letters.[7, 8, 37] One study found that more than half of patients who received a new prescription for ICS filled it only once within the following year, suggesting

the need for early follow-up to promote adherence.[8] Excessive SABA use also has been associated with increased exacerbation risk and healthcare costs.[38] An intervention that involved sending letters to providers of patients with excessive SABA pharmacy fills resulted in lower SABA use in 67 percent of patients.[37] In an effort to promote optimal asthma management, the National Committee for Quality Assurance (NCQA) has developed quality measures for the treatment of asthma, against which health plan performance is graded. Payers are thus incentivized to use any resources necessary to ensure the highest-quality asthma care is delivered to their members. Despite the inherent limitations of using retrospective data, analysis of claims through use of such measures as the medication possession ratio (MPR), proportion of days covered (PDC), refill compliance rate (RCR), and continuous measure of medication gaps (CMG),[36] is invaluable to the improvement of asthma management on the population level.

Formulary changes: Health plans have increasingly moved toward two- and three-tier prescription drug plans to encourage the use of preferred drugs. Changing from a single- to a multi-tier structure can result in an increase in the utilization of preferred medications.[27] Conversely, the increase in patient cost-sharing through higher copayments may reduce access to certain medications for chronic illness.[27] Implementation of a more inclusive formulary structure that permits access to multiple agents within the same therapeutic class at comparable costs will encourage physicians and patients to choose the most appropriate agents,[27] compared with less-inclusive formularies that restrict access. There is no evidence, however, that enhanced inclusivity reduces nonadherence. Value-based insurance design (VBID), which focuses on decreasing patient cost-sharing for high-value services, is a strategy that has been utilized by health plans and employers with success.[39] When a large employer group in Texas piloted a program of reduced copayments for selected asthma medications (lowering the copayment from $20-$30 to $5), the group with the lower copayments had significantly better adherence to asthma control medication (53.9 percent) compared with patients whose copayments had not been changed (43.9 percent). In addition, reductions in medical costs in the low-copayment group offset the employer's higher pharmacy costs.[39] Other well-known examples of successful value-based systems of care delivery include Pitney Bowes and the Asheville Project. These results, however, have not been uniformly reproducible.

There are several ways to improve adherence to asthma medications, but an important consideration is that improving asthma quality of care and health outcomes requires a multifaceted approach. A review of 69 trials of interventions to improve asthma care and adherence found that the most effective approaches included several components, such as educational information, reminders, counseling, supportive care, and telephone follow-up.[8] The intensive approaches supported in the literature often require substantial investment of resources, which can be a major challenge for many organizations. Nonetheless, even simple interventions, such as telephone contacts, can produce improvements and tend to be cost-effective.[8]

Stepping Stones to Better Care

The use of daily controller medication is the cornerstone of good asthma management, yet poor adherence to treatment is pervasive. Low adherence leads to suboptimal treatment, increased use of healthcare services, lower patient quality of life, and increased healthcare costs.[2, 12] A recent analysis of claims data from a large national insurer found that physicians prescribed ICS for persistent asthma 78 percent of the time, but their patients adhered to ICS therapy only 37 percent of the time.[40] Managed care organizations thus face an immense, multifaceted challenge in addressing the problem of nonadherence to asthma therapy.

Although there isn't a single intervention model that will work in all health systems and patient populations, a number of approaches and interventions have shown benefit while maintaining cost-effectiveness.[1, 16] Since there are several barriers to asthma medication adherence, implementing multiple strategies that intervene at the patient, provider, and health system levels can be more effective than single interventions.[16, 17] A stepwise approach that is based on careful planning and involves healthcare providers is most likely to succeed. A key starting point is to conduct a baseline analysis using administrative claims data to determine the scope of the adherence problem within the coverage network. Targeted strategies can then be tailored to the particular provider and patient audience. To determine feasible interventions, a review of successful examples of other employer-based and health plan-specific initiatives may be of benefit.

Involving allied health professionals in selecting and piloting interventions is critical for both cost-effectiveness and logistical reasons.[16] Many effective interventions

3,100

There are only about 3,100 Certified Asthma Educators nationally, compared to 24 million Americans living with asthma.

utilize pharmacists, as their regular access to patients offers an excellent opportunity for the provision of asthma counseling. Certified asthma educators are also a valuable resource, due to their specialized training and expertise in the provision of asthma education.[1, 15-18] The inclusion of patient-centric interventions that address specific barriers is also crucial to improving asthma controller medication adherence.[8, 16] Changes at the system and organizational levels have the potential to substantially impact asthma management and patient adherence. Before implementing widespread VBID interventions, demonstrate preliminary successes and cost-effectiveness through pilot programs with select employer groups.

Solving asthma adherence issues is challenging, but given the increasing burden that this highly prevalent disease places on the healthcare system, there is a growing urgency to identify and implement feasible, cost-effective interventions.

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In patients with type 2 diabetes, the TITRATE® study demonstrates

Once-daily Levemir® gets the majority of patients to goal safely[1]

64% of patients achieved A1C goal <7% with once-daily Levemir®*

The Levemir® TITRATE trial shows how a majority of patients with type 2 diabetes taking a basal insulin, some with A1C levels as high as 9%, achieved the ADA-recommended target of A1C <7%.[1,2] Patients experienced a mean A1C decrease of –1.2%* and achieved goal safely with low rates of hypoglycemia, nearly all of which were minor or symptoms only.[1†]

*70 to 90 mg/dL group.

Model is for illustrative purposes only.

To see how Levemir® can help your patients achieve their goals, and to learn more about TITRATE, visit TITRATEstudy.com.

†Minor hypoglycemia rates were 0.42 (70-90 mg/dL) and 0.26 (80-110 mg/dL) per patient-month. A single major hypoglycemic event was reported in the 70 to 90 mg/dL group; no major hypoglycemic events in the 80 to 110 mg/dL group.[1]

Results from a 20-week, randomized, controlled, multicenter, open-label, parallel-group, treat-to-target trial using the PREDICTIVE® 303 self-titration algorithm in insulin-naive patients with type 2 diabetes, A1C ≥7% and ≤9% on OAD therapy randomized to Levemir® and OAD (1:1) to 2 different FPG titration targets (70-90 mg/dL [n=121] or 80-110 mg/dL [n=122]).[1]

PREDICTIVE = Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation.

Indications and usage

Levemir® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Important safety information

Levemir® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Levemir® should not be diluted or mixed with any other insulin preparations.

Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir®. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Levemir® is not to be used in insulin infusion pumps. Any change of insulin dose should be made cautiously and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.

Needles and Levemir® FlexPen® must not be shared.

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir® from other intermediate or long-acting insulin preparations. The dose of Levemir® may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation. Less common but more serious are severe cases of generalized allergy, including anaphylactic reaction, which may be life threatening.

Please see brief summary of Prescribing Information on adjacent page.

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Levemir®

insulin detemir (rDNA origin) injection

novo nordisk®

Levemir® (insulin detemir [rDNA origin] injection)

Rx ONLY

BRIEF SUMMARY. Please see package insert for full prescribing information.

INDICATIONS AND USAGE: LEVEMIR® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS: LEVEMIR® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

WARNINGS: Hypoglycemia is the most common adverse effect of insulin therapy, including LEVEMIR®. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes. LEVEMIR® is not to be used in insulin infusion pumps. Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted. Needles and LEVEMIR® FlexPen® must not be shared.

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.

Date of Issue: July 15, 2009
Version: 5

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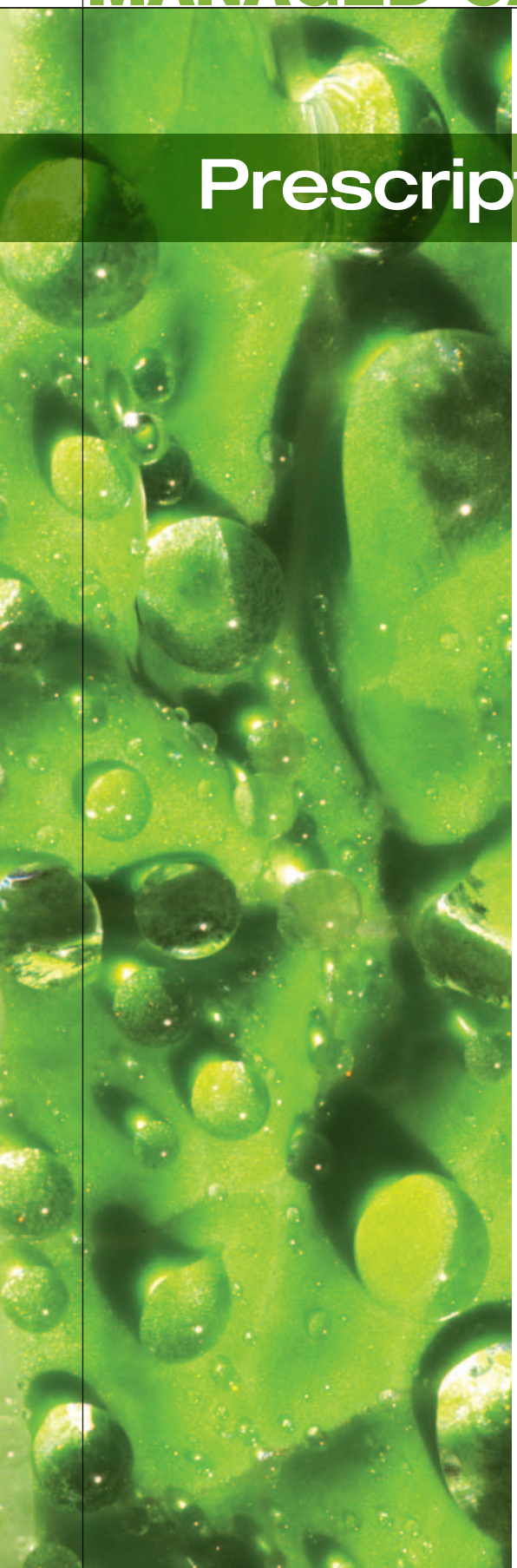
novo nordisk®

Levemir®
insulin detemir (rDNA origin) injection



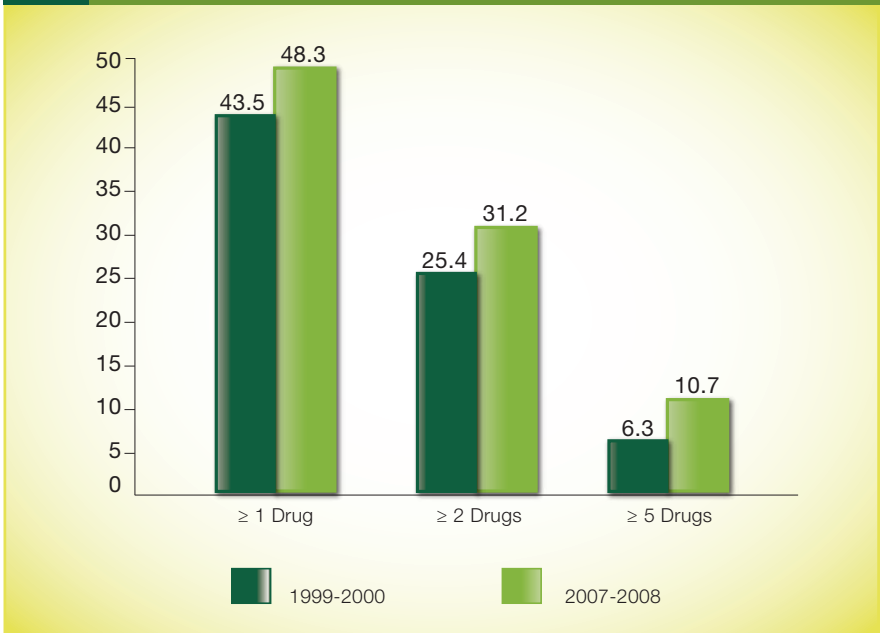
Prescription Drug Trends

Prescription medications are vital to the treatment of disease and maintenance of a healthy population, and are the mainstay of therapy for a multitude of conditions.

Advances in technology and research over the past decade have resulted in increased discovery of new molecular entities and therapies, with corresponding increases in prescription drug expenditures. According to a recent (September 2010) National Center for Health Statistics (NCHS) data brief on prescription drug data from the National Health and Nutrition Examination Survey (NHANES), prescription drug spending in the United States was $234.1 billion in 2008. This spending figure is greater than twice that observed in 1999.

The NHANES data presented in the NCHS data brief, "Prescription Drug Use Continues to Increase: U.S. Prescription Drug Data for 2007-2008," also indicates increases in the percentages of persons using any number of prescription drugs. Compared with 1999-2000, the number of people using at least one prescription drug in the past month during 2007-2008 increased about 4 percent; the number using two or more drugs increased about 6 percent; and the number using five or more drugs increased about 5 percent (see Figure 1).

Fig. 1 **PERCENTAGE OF PERSONS USING PRESCRIPTION DRUGS, 1999-2000 VS. 2007-2008**



As one would expect, the demographic with the highest usage of multiple prescription medications was the senior population. More than 76 percent of Americans ages 60 and older used at least two prescription drugs, and 37 percent used five or more, supporting the notion that prescription drug use increases with advancing age.

The most commonly used drug categories varied by age demographic among Americans in 2007-2008 (see Figure 2). Bronchodilators for asthma were the predominant drug class used by children ages 0-11, with CNS stimulants for attention-deficit disorder (ADD) having the highest utilization among ages 12-19. The most frequently used medications among adults aged 20-59 were antidepressants, and cholesterol-lowering medications for adults ages 60 and older. Also important to note is that for children less than 6 years old, penicillin antibiotics were the most common.

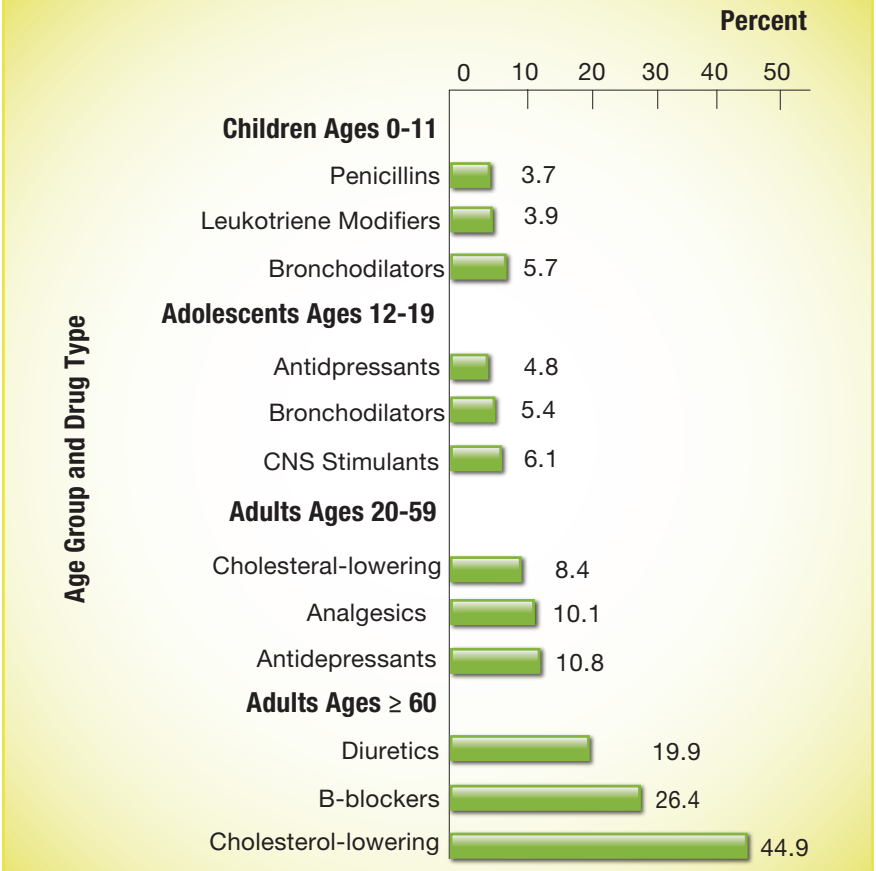
Despite the overall growth in spending on prescriptions over the last decade, medication nonadherence remains a problem. According to a 2009 report by the New England Healthcare Institute (NEHI), upward of $290 billion per year, or approximately 13 percent of total healthcare costs, is incurred in unnecessary and avoidable expenditures attributable to varying degrees of nonadherence.[2] This underscores the pressing need for widespread implementation of interventions aimed at improving appropriate prescribing, initial fulfillment, proper use of medication, and continued persistence with therapy.

$290 billion

$290 billion per year is incurred in unnecessary and avoidable expenditures attributable to nonadherence.

Fig. 2

MOST COMMONLY USED PRESCRIPTION DRUGS BY AGE GROUP, 2007-2008



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GLP-1 Agonists and the Changing Landscape of Type 2 Diabetes Treatment

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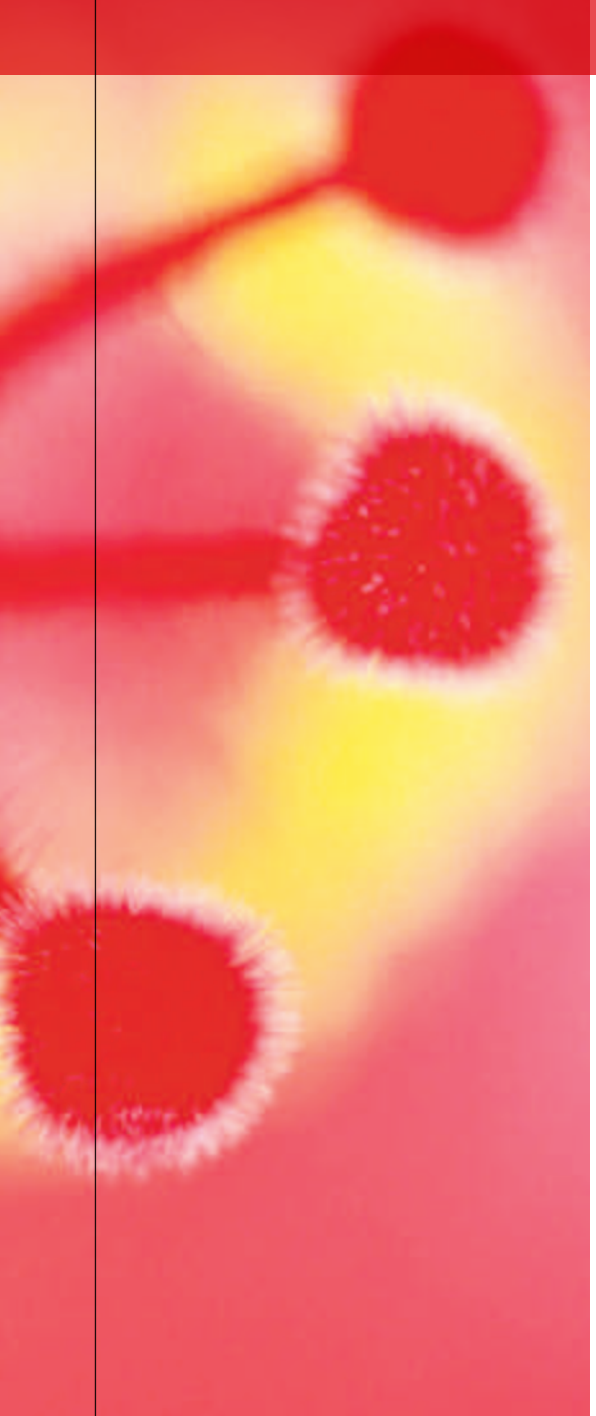

The glucagon-like-peptide-1 (GLP-1) agonists are a class of medications used to improve glycemic control in patients with Type 2 Diabetes Mellitus (T2DM).[1] There are currently only two GLP-1 agonists available in the United States,[1, 2] but several others are in phase III trials and could receive approval in the near future.[3]

GLP-1 agonists were introduced to the American diabetes market in 2005 with the United States Food and Drug Administration (FDA) approval of exenatide (Byetta®). More recently, liraglutide (Victoza®) was approved in early 2010. GLP-1 agonists are commonly used in conjunction with other diabetes medications, such as metformin, and in some situations, may be used as monotherapy.[4-6] Similar to other peptide drugs, GLP-1 agonists require injection. They are injected subcutaneously once or twice daily, depending on the particular GLP-1 agonist.

Aside from improving glycemic control, GLP-1 agonists also promote delayed gastric emptying and weight loss.[4] Weight loss is particularly desirable in T2DM patients, as many of them are obese and other diabetes medications can cause weight gain (such as the thiazolidinediones [TZDs]). GLP-1 agonists, similar to metformin, can commonly cause gastrointestinal side effects, particularly nausea.[1, 2, 7] Nausea incidence rates in GLP-1 agonist monotherapy trials have ranged from 8 to 28 percent, whereas in metformin trials they have ranged from 7 to 26 percent. For both agents, these effects are usually self-limiting and resolve over time. Hypoglycemia is not particularly problematic with GLP-1 agonists—unlike some other diabetes medication classes—unless used in combination with other medications that can cause hypoglycemia, such as sulfonylureas.

Clinical and Safety Considerations

GLP-1 agonists are approved by the FDA as adjuncts to diet and exercise to improve glycemic control in adults with T2DM.[1, 2] They are not currently approved for use in conjunction with insulin therapy, but a supplemental New Drug Application (sNDA) has recently been filed for such use with exenatide.[8] Current guidelines generally recommend the use of GLP-1 agonists as an option for adjunctive therapy after metformin monotherapy has failed.[4,5] The American Diabetes Association (ADA) treatment guidelines, last updated in 2008, place GLP-1 agonist

Fig. 1 **COMPARATIVE HbA_{1c} REDUCTION VS. ORAL THERAPIES**

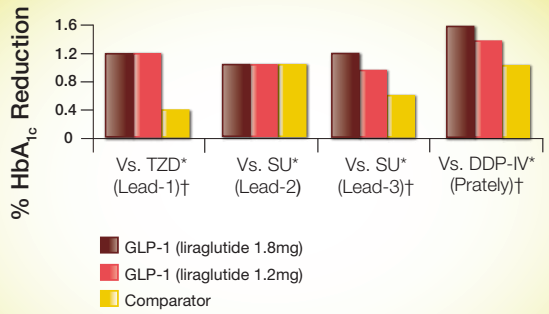

Figure 1: Comparative HbA_{1c} Reductions vs. Oral Therapies [11, 13, 15]
* TZD used was rosiglitazone, SU used was glimepiride, and DPP-IV used was sitagliptin.
† Significant HbA_{1c} reduction in favor of liraglutide (both doses).

Fig. 2 **COMPARATIVE HbA_{1c} REDUCTION VS. BASAL INSULIN**

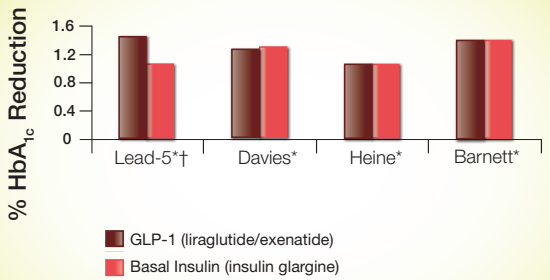

Figure 2: Comparative HbA_{1c} Reductions vs. Basal Insulin [17, 23, 25, 26]
* Lead-5 used liraglutide 1.8mg; Davies, Heine, and Barnett used exenatide 10mg.
† Significant HbA_{1c} reduction in favor of the GLP-1 agonist.

therapy under their "Tier 2: less well-validated therapies."[5] However, the ADA guidelines highlight GLP-1 agonists as an option when hypoglycemia is of particular concern and weight loss is desired. The American Association of Clinical Endocrinologists (AACE) treatment algorithm (2009) has a stronger recommendation for GLP-1 agonist therapy.[4] In fact, when dual therapy is indicated, the AACE algorithm considers GLP-1 agonists the preferred class due to their HbA_{1c} reduction potential, weight reduction, and low risk for hypoglycemia. This reflects the importance of using medications that complement existing therapies through their unique and diverse mechanisms of action.

GLP-1 agonists activate the GLP-1 receptor, stimulate insulin secretion, and reduce glucagon secretion in a glucose-dependent manner, which helps explain their minimal risk for hypoglycemia.[1, 2] GLP-1 agonists and DPP-IV inhibitors (such as sitagliptin; [Januvia®] and saxagliptin; [Onglyza™]) are commonly associated with one another due to their similar mechanisms of action.[9] Both classes share the desirable characteristic of having minimal hypoglycemia risk, but notable differences do exist between the two. The DPP-IV inhibitors do not have as much of a reduction on HbA_{1c} or weight loss as the GLP-1 agonists, but they do not typically cause nausea and do not require injection. The pharmacodynamic differences between the GLP-1 agonists and DPP-IV inhibitors are likely related to minor differences in their mechanisms of action; DPP-IV inhibitors only increase the amount of available endogenous GLP-1, whereas GLP-1 agonists are estimated to increase GLP-1 receptor activity to a much greater degree.

Winston Wong, PharmD

As with most diabetes medications, the efficacy of GLP-1 agonists is typically measured by HbA_{1c} reduction. Most clinical trials have demonstrated HbA_{1c} reductions of 0.75 to 1.5 percent over 28 weeks, depending on the GLP-1 agonist used, the dose, and concurrent therapy.[9-35] Many of these studies directly evaluated GLP-1 agonist therapy with comparator agents from other common drug classes, such as DPP-IV inhibitors, TZDs, and sulfonylureas; GLP-1 agonists consistently demonstrated superiority or noninferiority with regard to HbA_{1c} reduction (see Figure 1). They have also been shown to be noninferior to insulin therapy in many trials, and in at least one trial, superior HbA_{1c} reduction was exhibited with GLP-1 agonist therapy (see Figure 2).[17, 23, 25, 26] Trials of longer duration have illustrated that GLP-1 agonists possess the ability to maintain their efficacy for a period of at least two years.[33, 35]

Due to the ability of GLP-1 agonists to promote weight loss, investigational research is being conducted to analyze their effects in obese, non-diabetic patients. One completed trial found the GLP-1 agonist liraglutide caused significantly more weight loss versus placebo and the obesity drug

Table 1 ADVANTAGES AND DISADVANTAGES OF SEVERAL T2DM MEDICATION CLASSES.[4, 5, 48]

Drug Class	Advantages	Disadvantages	Expected HbA_{1c} Reductions
Biguanides (metformin)	First-line treatment, weight loss, low hypoglycemia risk, inexpensive	Not recommended with renal and liver impairment, GI effects	1–2%
DPP-IV Inhibitors	Well tolerated, low hypoglycemia risk	No generic availability	0.5–0.8%
GLP-1 Agonists	Weight loss, low hypoglycemia risk	Requires injection, GI effects, no generic availability	0.5–1.5%
Sulfonylureas	Long history of use, inexpensive	Hypoglycemia, weight gain	1–2%
Thiazolidinediones	Low hypoglycemia risk	Weight gain, cardiovascular risks with rosiglitazone, no generic availability	0.5–1.4%

orlistat.[36] GLP-1 agonists may also offer cardiovascular benefits, as several small trials have demonstrated.[37] Larger trials are currently ongoing to better evaluate and understand the effect of GLP-1 agonists on cardiovascular comorbidities.

Long-term safety has not been thoroughly established for the GLP-1 agonists, as they have only been in public use for six years. In 2007, the FDA voiced concerns over a possible association between GLP-1 agonist use and pancreatitis and required studies to analyze the possible link.[38] There is question as to whether the increased risk for pancreatitis is due to GLP-1 therapy or the presence of T2DM; thus far, research has not found an association between GLP-1 agonists and pancreatitis.[39] Liraglutide has a boxed warning due to an increased incidence of thyroid tumors observed in rodent studies, but no association has been observed in humans.[2]

Impact of GLP-1 Agonists on the Diabetes Market Dynamic

A major benefit of the addition of new drug classes for T2DM is the expansion of treatment choices for patients and their providers. Each patient and physician has individual concerns and preferences that influence clinical decision making. Despite the clear efficacy of GLP-1 agonists in improving glycemic control, therapeutic advantages over other medication classes (see Table 1), and recommendations from national guidelines, they have not been as extensively utilized as other drug therapies for T2DM. It was recently estimated that, as of the third quarter of 2010, GLP-1 agonists constituted only 4.2 percent of the entire diabetes market.[40] It may be that their route of administration has deterred prescribers and patients from embracing them as an early option in dual therapy. Perhaps the need for injection has caused GLP-1 agonists to be correlated with insulin therapy, which is typically viewed by T2DM patients and their providers as a medication of last resort. For example, a patient with a strong fear of needles might be wary of initiating treatment with a GLP-1 agonist, while physicians who advocate for stepwise management using oral agents as single, dual, or triple therapy may be less inclined to use an injectable as a preferred component of the regimen. However, other

4.2%

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individuals may find the many advantages offered by GLP-1 agonists, such as weight loss and minimal risk of hypoglycemia, to outweigh any potential detractors. For example, a recent study found greater treatment satisfaction among patients randomized to liraglutide therapy compared with those randomized to sitagliptin,[41] indicating that these preconceptions about treatment are obstacles that can be overcome.

Continued advances in GLP-1 agonist research and development to address their potential shortcomings are likely to bring the drug class even further into the mainstream of diabetes treatment. The recent FDA-approval of liraglutide brings an enhancement to GLP-1 agonists: once-daily dosing without regard to food. Previously, exenatide, which requires twice-daily dosing before meals, was the only GLP-1 agonist available. Recognizing their potential as cornerstones of T2DM treatment, many manufacturers are developing GLP-1 agonists with varying dosing frequencies. The FDA postponed the approval of a once-weekly formulation of exenatide last October, citing the need for additional safety and efficacy data,[42] but other once-weekly formulations of GLP-1 agonists are currently undergoing testing in late-phase trials.[3] There is also an additional once-daily GLP-1 agonist in phase III trials. In an effort to address potential concerns over the need for injection, an oral GLP-1 agonist is under development and has recently begun testing in early-phase trials.

In light of the potential approval of additional GLP-1 agonists and the pressing need for medications with diverse mechanisms of action and therapeutic profiles, it is likely that this medication class will be more greatly utilized in the near future. Although the GLP-1 agonist share of the overall market is relatively small when compared with agents such as metformin and sulfonylureas, the approval of liraglutide was associated with an almost 30 percent increase in overall GLP-1 agonist market share in less than a year.[40] With such an impact likely being attributed to the availability of a once-daily agent, further advances in product formulation could foster additional increases in GLP-1 agonist utilization, popularity, and perceived value among payers. This, coupled with future clinical data that may support expanding the use of GLP-1 agonists to other conditions such as obesity, means that GLP-1 agonists will likely be relevant for years to come.

Implications for Managed Care

Health plans and managed care organizations play a role in prescription drug utilization, as reimbursement and patient cost-sharing structures impact treatment decisions on a regular basis. Many traditional formularies, particularly those for diabetes medications, rely on using step-therapy to "appropriately" manage the prescription drug benefit. This often entails using low-cost generics first-line to control drug expenditures, before moving toward newer brand-name agents. Many plans may require a patient to try and fail therapy with a certain number of oral agents before granting coverage for a newer and more expensive drug, such as a GLP-1 agonist, via prior authorizations or other policy controls. Administering a prescription drug benefit requires the maintenance of an ever-delicate balance between the clinical and cost profiles of drugs. Unfortunately, many of the stepped approaches to formulary management may struggle to stay current with advances in diabetes therapy by placing too great of an emphasis on the cost side of the scale, thus devaluing any potential clinical innovations offered by newer agents.

This seems to be particularly true for GLP-1 agonists. A recent poll of managed care executives, representing organizations that provide pharmacy benefits for upwards of 10 million commercial lives, examined how they value different diabetes medication classes. The most common response for GLP-1 agonists ranked them sixth out of the eight classes that were listed.[43] Since cost is an influential factor in the formulary decision-making process, it is possible that the higher drug costs of GLP-1 agonists relative to more inexpensive generic therapy options, such as the sulfonylureas, may negatively impact the perception of their overall value.

Direct medication costs, however, are only a small part of the overall cost equation. This is evidenced by the substantial societal burden of diabetes, much of which is attributable to complications that could be directly ameliorated through greater patient adherence to therapy. Frequently cited reasons for nonadherence to antidiabetic medications include, among others, fear of hypoglycemia and weight gain, which are caused by such commonly used agents as sulfonylureas and insulin. The availability of GLP-1 agonists may help patients with such concerns better adhere to their therapies. Providing coverage for multiple treatment options at reasonable levels of cost-sharing can assist patient-centered care, which may increase adherence and thus improve overall outcomes.[44]

It has also been demonstrated that medication adherence declines as the complexity of a patient's treatment regimen increases, and plans may be inadvertently contributing to nonadherence by emphasizing the use of multiple oral agents as preferred treatment. Due to the progressive nature of the diabetes disease course, most initial treatment regimens are insufficient to gain adequate and sustained control, and more intensive management is eventually warranted. Hence, there has been increasing focus on the use of more aggressive interventions earlier in the disease course to provide a greater likelihood of improved outcomes. Unfortunately, clinical inertia on the part of the provider and patient often impedes the use of such treatment earlier in the course of therapy. Conservative managed care approaches to administering diabetes formularies may propagate this clinical inertia by delaying use of newer (and hence, more expensive) drugs until numerous failures with other agents have occurred. It is important for managed care organizations to avoid "paralysis by analysis" in waiting for extensive, long-term studies that demonstrate improvements in overall morbidity and mortality rates for new medications before including them in treatment algorithms. As we are reminded by data from the United Kingdom Prospective Diabetes Study (UKPDS), reductions in HbA_{1c} levels are associated with reductions in microvascular complications and risk of diabetes-related death;[45] hence, the introduction of new therapies that enhance the likelihood of getting more patients to HbA_{1c} goals should be welcomed.

There is a recognized need among patients, providers, and payers alike for clinically innovative medications to effectively treat the growing number of people with diabetes.

There is a recognized need among patients, providers, and payers alike for clinically innovative medications to effectively treat the growing number of people with diabetes. The Centers for Disease Control and Prevention (CDC) estimates that almost 26 million Americans have the disease.[46] These numbers are of epidemic proportions and are rapidly on the rise. In fact, the CDC estimates that by 2050, 1 in 3 American adults could have diabetes.[47] With an increasing number of Americans living with the disease, it is vital to have a multitude of treatment options available for these individuals to enhance the likelihood of favorable outcomes and reduce the burden on our healthcare system.

GLP-1 agonists are the latest class of medications available to aid in this ongoing struggle. They offer a distinct and complementary mechanism of action that offers measurable improvements in HbA_{1c} levels when used as either monotherapy or in combination with other agents. In fact, GLP-1 agonists have consistently demonstrated superior HbA_{1c}-lowering capabilities compared with some other treatment mainstays, such as sulfonylureas and TZDs. Despite potential drawbacks, such as need for injection, GI side effects, and boxed warnings, GLP-1 agonists possess many therapeutic traits that favorably distinguish them from other traditional therapies. They offer little risk of hypoglycemia and actually cause weight loss, addressing two major concerns posed by widely used T2DM treatment options, such as sulfonylureas and insulin. There is also evidence to support a potential modest benefit on cardiovascular measures, such as lipid profiles. These considerations have fueled industry interest in the class, as evidenced by numerous manufacturers with GLP-1 agonists in the pipeline. Patients and providers have also recognized the value of this novel medication class, as GLP-1 agonist utilization has been on the rise following the recent release of once-daily liraglutide. Expert panels, such as the American Association of Clinical Endocrinologists, have advocated for GLP-1 agonists as a preferred treatment option in T2DM, ahead of such mainstays of treatment as the sulfonylureas.

It will be interesting to witness the evolution of the GLP-1 agonist market over the next few years, how they will be valued amongst other diabetic medication classes, and where they will be placed in future treatment guidelines and algorithms. Presently, the evidence supports the GLP-1 agonist class as a beneficial addition to the diabetes treatment armamentarium. All that remains is for managed care to recognize their value and view them as viable options in the treatment of T2DM, not solely as high-cost medications reserved for cases of treatment failure.

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VIMOVO–the only prescription-strength NSAID therapy with a built-in PPI for

Rx pain relief treatment for osteoarthritis patients at risk of NSAID-associated gastric ulcers.[1]

In clinical trials, up to 96% of patients did not have a gastric ulcer detected[1,2]

- Results for the low-dose aspirin (LDA) subgroup were consistent with the overall findings of the study[1]
  - — The LDA subgroup comprised approximately 25% of the overall study population (n=201)[1,2]
  - — VIMOVO can be administered with low-dose aspirin (≤325 mg/day). The concurrent use of aspirin and VIMOVO may increase the risk of serious adverse events. As with other NSAIDs, concurrent administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse events

Visit www.VIMOVO.com to learn more.
For the clinical monograph, go to www.PTcommunity.com

As with all NSAIDs, use the lowest effective dose for the shortest duration of time consistent with individual patient treatment goals.

VIMOVO is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

Vimovo™
(naproxen/esomeprazole magnesium)
375/20•500/20 mg delayed-release tablets

Important Safety Information

Cardiovascular Risk

- **Naproxen, a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.**
- **VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.**

Gastrointestinal Risk

- **NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events.**

The most commonly observed adverse events in clinical trials (experienced by >5% patients in the VIMOVO group) were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, and nausea.

Please see Brief Summary of Prescribing Information, including Boxed Warnings, on adjacent pages.

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AstraZeneca

Vimovo™

naproxen/esomeprazole magnesium

delayed-release tablets

BRIEF SUMMARY of Prescribing Information.

Cardiovascular Risk

- **NonSteroidal Anti-inflammatory Drugs (NSAIDs), a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see *Warnings and Precautions*].**
- **VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications*, and *Warnings and Precautions*].**

Gastrointestinal Risk

- **NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see *Warnings and Precautions*].**

INDICATIONS AND USAGE

VIMOVO is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of VIMOVO and other treatment options before deciding to use VIMOVO. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. VIMOVO does not allow for administration of a lower daily dose of esomeprazole. If a dose of esomeprazole lower than a total daily dose of 40 mg is more appropriate, a different treatment should be considered.

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

The dosage is one tablet twice daily of VIMOVO 375 mg naproxen and 20 mg of esomeprazole or 500 mg naproxen and 20 mg of esomeprazole.

The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet. VIMOVO is to be taken at least 30 minutes before meals.

Geriatric Patients Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Use caution when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly use the lowest effective dose [see **Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Patients With Moderate to Severe Renal Impairment Naproxen-containing products are not recommended for use in patients with moderate to severe or severe renal impairment (creatinine clearance <30 mL/min). [see **Warnings and Precautions** and **Use in Specific Populations**].

Hepatic Insufficiency Monitor patients with mild to moderate hepatic impairment closely and consider a possible dose reduction based on the naproxen component of VIMOVO.

VIMOVO is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Warnings and Precautions**, **Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Pediatric Patients The safety and efficacy of VIMOVO in children younger than 18 years has not been established. VIMOVO is therefore not recommended for use in children.

CONTRAINDICATIONS

VIMOVO is contraindicated in patients with known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any of the excipients.

VIMOVO is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [see **Warnings and Precautions**]. Hypersensitivity reactions, eg, angioedema and anaphylactic reaction/shock, have been reported with esomeprazole use.

VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see **Warnings and Precautions**].

VIMOVO is contraindicated in patients in the late stages of pregnancy [see **Warnings and Precautions** and **Use in Specific Populations**].

WARNINGS AND PRECAUTIONS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDS, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see **Contraindications**].

Hypertension

NSAIDs, including naproxen, a component of VIMOVO, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy [see **Drug Interactions**].

Congestive Heart Failure and Edema

Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs and should be used with caution in patients with fluid retention, or heart failure.

Gastrointestinal Effects — Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including naproxen, a component of VIMOVO, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. While VIMOVO has been shown to significantly decrease the occurrence of gastric ulcers compared to naproxen alone, ulceration and associated complications can still occur.

These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed.

VIMOVO should be prescribed with caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk of developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants or antiplatelets (including low-dose aspirin), longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID or NSAID-containing product, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of an NSAID, COX-2 inhibitor, or aspirin potentiated the risk of bleeding [see **Drug Interactions**]. Although these studies focused on upper gastrointestinal bleeding, bleeding at other sites cannot be ruled out.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Gastrointestinal symptomatic response to therapy with VIMOVO does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long- term with omeprazole, of which esomeprazole is an enantiomer and a component of VIMOVO.

Active Bleeding

When active and clinically significant bleeding from any source occurs in patients receiving VIMOVO, the treatment should be withdrawn.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of VIMOVO in patients with advanced renal disease. Therefore, treatment with VIMOVO is not recommended in these patients with advanced renal disease. If VIMOVO therapy must be initiated, close monitoring of the patient's renal function is advisable [see **Dosage and Administration, Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Anaphylactoid Reactions

Anaphylactoid reactions may occur in patients without known prior exposure to either component of VIMOVO. NSAIDs should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [see **Contraindications**]. Emergency help should be sought in cases where an anaphylactoid reaction occurs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Skin Reactions

NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

Pregnancy Category C–In late pregnancy, as with other NSAIDs, naproxen, a component of VIMOVO should be avoided because it may cause premature closure of the ductus arteriosus [see **Contraindications** and **Use in Specific Populations**].

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including naproxen, a component of VIMOVO. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with VIMOVO. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), VIMOVO should be discontinued.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose for the shortest possible duration of adequate treatment.

VIMOVO is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Dosage and Administration**, and **Use in Specific Populations**].

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving VIMOVO who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants or antiplatelets, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VIMOVO should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Concomitant NSAID Use

VIMOVO contains naproxen as one of its active ingredients. It should not be used with other naproxen-containing products since they all circulate in the plasma as the naproxen anion.

The concomitant use of VIMOVO with any dose of a nonaspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

Corticosteroid Treatment
VIMOVO cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Bone Fracture
Several studies and literature reports indicate that proton pump inhibitor (PPI) therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Those patients with the highest risk received high-dose or long-term PPI therapy (a year or longer). Patients should use the lowest effective dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines. Adequate vitamin D and calcium intake is recommended.

Masking of Inflammation and Fever
The pharmacological activity of VIMOVO in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, VIMOVO should be discontinued.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

ADVERSE REACTIONS
Clinical Studies 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 adverse reactions reported below are specific to the clinical trials with VIMOVO. See also the full prescribing information for naproxen/esomeprazole magnesium products.

The safety of VIMOVO was evaluated in clinical studies involving 2317 patients (aged 27 to 90 years) and ranging from 3–12 months. Patients received either 500 mg/20 mg of VIMOVO twice daily (n=1157), 500 mg of enteric-coated naproxen twice daily (n=426), or placebo (n=246). The average number of VIMOVO doses taken over 12 months was 696±44.

The table below lists all adverse reactions, regardless of causality, occurring in >2% of patients receiving VIMOVO from two clinical studies (Study 1 and Study 2). Both of these studies were randomized, multi-center, double-blind, parallel studies. The majority of patients were female (67%), white (86%). The majority of patients were 50-69 years of age (83%). Approximately one quarter were on low-dose aspirin.

Table 1: Adverse Reactions Occurring in Patients >2% Study 1 and Study 2 (Endoscopic Studies)

Preferred Term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=428) %	EC-Naproxen 500 mg twice daily (n=426) %
Gastrointestinal Disorders		
Gastritis Erosive	19	38
Dyspepsia	18	27
Gastritis	17	14
Diarrhea	6	5
Gastric Ulcer	6	24
Abdominal Pain Upper	6	9
Nausea	5	5
Hiatus Hernia	4	6
Abdominal Distension	4	4
Flatulence	4	3
Esophagitis	4	8
Constipation	3	3
Abdominal Pain	2	2
Erosive Duodenitis	2	12
Abdominal Pain Lower	2	3
Duodenitis	1	7
Gastritis Hemorrhagic	1	2
Gastroesophageal Reflux Disease	<1	4
Duodenal Ulcer	<1	5
Erosive Esophagitis	<1	6
Infections and Infestations		
Upper Respiratory Tract Infection	5	4
Bronchitis	2	2
Urinary Tract Infection	2	1
Sinusitis	2	2
Nasopharyngitis	<1	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1	2
Nervous System Disorders		
Headache	3	1
Dysgeusia	2	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2	3

In Study 1 and Study 2, patients taking VIMOVO had fewer premature discontinuations due to adverse reactions compared to patients taking enteric-coated naproxen alone (7.9% vs. 12.5% respectively). The most common reasons for discontinuations due to adverse events in the VIMOVO treatment group were upper abdominal pain (1.2%, n=5), duodenal ulcer (0.7%, n=3) and erosive gastritis (0.7%, n=3). Among patients receiving enteric-coated naproxen, the most common reasons for discontinuations due to adverse events were duodenal ulcer 5.4% (n=23), dyspepsia 2.8% (n=12), and upper abdominal pain 1.2% (n=5). The proportion of patients discontinuing treatment due to any upper gastrointestinal adverse events (including duodenal ulcers) in patients treated with VIMOVO was 4% compared to 12% for patients taking enteric-coated naproxen.

The table below lists all adverse reactions, regardless of causality, occurring in >2% of patients from 2 clinical studies conducted in patients with osteoarthritis of the knee (Study 3 and Study 4).

Table 2: Adverse Reactions Occurring in Patients >2% (Study 3 and Study 4)

Preferred Term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=490) %	Placebo (n=246) %
Gastrointestinal Disorders		
Dyspepsia	8	12
Diarrhea	6	4
Abdominal Pain Upper	4	3
Constipation	4	1
Nausea	4	4
Nervous System Disorders		
Dizziness	3	2
Headache	3	5
General Disorders and Administration Site Conditions		
Peripheral Edema	3	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1	3
Infections and Infestations		
Sinusitis	1	2

The percentage of subjects who withdrew from the VIMOVO treatment group in these studies due to treatment-emergent adverse events was 7%. There were no preferred terms in which more than 1% of subjects withdrew from any treatment group.

The long-term safety of VIMOVO was evaluated in an open-label clinical trial of 239 patients, of which 135 patients received 500 mg/20 mg of VIMOVO for 12 months. There were no differences in frequency or types of adverse reactions seen in the long-term safety study compared to shorter-term treatment in the randomized controlled studies.

Postmarketing Experience
Naproxen The following adverse reactions have been identified during post-approval use of naproxen. 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. These reports are listed below by body system. **Body as a Whole:** anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever); **Cardiovascular:** congestive heart failure, vasculitis, hypertension, pulmonary edema; **Gastrointestinal:** gastrointestinal bleeding and/or perforation, hematemesis, pancreatitis, vomiting, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, ulcerative stomatitis, esophagitis, peptic ulceration; **Hepatobiliary:** jaundice, abnormal liver function tests, hepatitis (some cases have been fatal); **Hemic and Lymphatic:** eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia; **Metabolic and Nutritional:** hyperglycemia, hypoglycemia; **Nervous System:** inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions; **Respiratory:** eosinophilic pneumonitis, asthma; **Dermatologic:** alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematosus, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored. **Special Senses:** hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema; **Urogenital:** glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine; **Reproduction (female)**: infertility.

Esomeprazole The following adverse reactions have been identified during post-approval use of esomeprazole. 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. These reports are listed below by body system. **Blood and Lymphatic:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastrointestinal:** pancreatitis, stomatitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; **Metabolism and Nutritional Disorders:** hypomagnesemia; **Musculoskeletal and Connective Tissue:** muscular weakness, myalgia; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal and Urinary:** interstitial nephritis; **Reproductive System and Breast:** gynecomastia; **Respiratory, Thoracic, and Mediastinal:** bronchospasm; **Skin and Subcutaneous Tissue:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS
Several studies conducted with VIMOVO have shown no interaction between the two components, naproxen and esomeprazole.

ACE-inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking VIMOVO concomitantly with ACE-inhibitors.

Aspirin
VIMOVO can be administered with low-dose aspirin (≤325 mg/day) therapy. The concurrent use of aspirin and VIMOVO may increase the risk of serious adverse events. [see **Warnings and Precautions**, **Adverse Reactions**, and **Clinical Studies** (14) in full Prescribing Information].

When naproxen is administered with doses of aspirin (>1 gram/day), its protein binding is reduced. The clinical significance of this interaction is not known. However, as with other NSAIDs, concomitant administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Cholestyramine
As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics
Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely both for signs of renal failure, as well as to monitor to assure diuretic efficacy [see **Warnings and Precautions**].

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Anticoagulants

Naproxen decreases platelet aggregation and may prolong bleeding time.

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Postmarketing reports of changes in prothrombin measures have been reported among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs including COX-2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with SSRIs [see **Warnings and Precautions**].

Other Information Concerning Drug Interactions

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, hydantoins, and other NSAIDs. Patients simultaneously receiving VIMOVO and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Drug/Laboratory Test Interaction

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Interactions Related to Absorption

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts, and digoxin).

Antiretroviral Agents

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors such as esomeprazole is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Omeprazole, the racemate of esomeprazole, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg once a day), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and main oxidative metabolite, hydroxy-*t*-butylamide (M8). Following multiple doses of atazanavir (400 mg, once a day) and omeprazole (40 mg, once a day, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported with an increase in AUC by 82% in C_{max} by 75% and in C_{min} by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice a day for 15 days with omeprazole 40 mg once a day coadministered on days 11 to 15). Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some anti-retroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.

However, postmarketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in crossover study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above-mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Other Pharmacokinetic-based Interactions

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine does not seem to change the pharmacokinetic profile of esomeprazole.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.

Starting at 30 weeks gestation, VIMOVO, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. VIMOVO can cause fetal harm when administered to a pregnant woman starting at 30-weeks gestation. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus. There are no adequate and well-controlled studies in pregnant women. Prior to 30-weeks gestation, VIMOVO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies with naproxen have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug [see **Animal Toxicology and/or Pharmacology** (13.2) in full Prescribing Information]. However, animal reproduction studies are not always predictive of human response.

Reproductive studies in rats and rabbits with esomeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are no adequate and well-controlled studies of esomeprazole use in pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Esomeprazole is the S-isomer of omeprazole. In four population-based cohort studies that included 1226 women exposed during the first trimester of pregnancy to omeprazole there was no increased risk of congenital anomalies.

Reproductive studies with esomeprazole have been performed in rats at doses up to 57 times the human dose and in rabbits at doses up to 35 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. [see **Animal Toxicology and/or Pharmacology** (13.2) in full Prescribing Information].

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. The effects of VIMOVO on labor and delivery in pregnant women are unknown.

Nursing Mothers

VIMOVO should not be used in nursing mothers due to the naproxen component.

Naproxen The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Esomeprazole The excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. However, omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for esomeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of VIMOVO has not been established in children younger than 18 years.

Geriatric Use

Of the total number of patients who received VIMOVO (n=1157) in clinical trials, 387 were ≥65 years of age, of which 85 patients were 75 years and over. No meaningful differences in efficacy or safety were observed between these subjects and younger subjects. [see **Adverse Reactions**].

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose [see **Dosage and Administration** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of NSAIDs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population [see **Warnings and Precautions**].

Naproxen is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of NSAIDs [see **Warnings and Precautions**].

Hepatic Insufficiency

VIMOVO is not recommended for use in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Dosage and Administration** and **Warnings and Precautions**].

Renal Insufficiency

Naproxen-containing products, including VIMOVO are not recommended for use in patients with advanced renal disease [see **Dosage and Administration** and **Warnings and Precautions**].

OVERDOSAGE

There is no clinical data on overdosage with VIMOVO.

Overdosage of Naproxen Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD50 of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

Overdosage of Esomeprazole A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - *Adverse Reactions*). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

If overexposure occurs, call the Poison Control Center at 1-800-222-1222.

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4/2010 301190

Medication Reconciliation: A Tool to Reduce Post-Discharge Resource Utilization

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One hospitalization alone is a costly venture. When coupled with preventable readmissions, an unnecessary burden is placed on our healthcare system.

Unfortunately, many Americans unnecessarily travel through this revolving door each year. According to a 2009 study in the *New England Journal of Medicine*, nearly 20 percent of Medicare patients hospitalized between 2003 and 2005 were readmitted within 30 days, while 34 percent were rehospitalized within 90 days. The estimated cost of those readmissions is extremely high—a staggering $17.4 billion.[1]

For managed care executives, reducing costly hospital utilization among recently discharged patients is essential to controlling escalating healthcare costs. Traditionally, hospitals may have experienced difficulties in developing and administering programs designed to reduce patient readmissions, and may have been either unwilling or unable to invest sufficient resources to overcome these barriers. However, due to potential changes in reimbursement and federally regulated patient safety measures, hospitals will now be penalized for inadequate patient care (see sidebar, page 43). This, coupled with the development of Accountable Care Organizations (ACOs), will encourage managed care executives to have an even greater emphasis on medication reconciliation.

As payers and hospitals further align their goals toward reducing readmissions, there is a strong focus on several potential areas of improvement. One strategy is to implement interventions aimed at reducing drug errors and medication nonadherence, as these are often substantial contributors to rehospitalization. A promising tool for tackling these issues is medication reconciliation.

Overview of Medication Reconciliation

Medication reconciliation involves the compilation of a complete and accurate list of a patient's current drug therapy and its comparison with the hospital's medical

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record. The list should include the name of the drug, dose, route, frequency, and purpose. All over-the-counter medications, dietary/herbal supplements, and prescription medications are included in the process, which enhances the ability of the hospital staff to prevent medication errors that may occur as a result of drug interactions, therapeutic duplication, improper dosing, or omission of necessary therapy.[2,3]

According to the Agency for Healthcare Research and Quality (AHRQ), the most common safety issues in hospitals are medication errors. Researchers estimate that more than 40 percent of these errors are the result of inadequate reconciliation at the stages of admission, in-hospital transfer, and discharge, and approximately 20 percent are deemed harmful to the patient.[3]

Medication reconciliation, however, may help prevent many of these errors. The process involves reviewing the patient's complete medication regimen at the critical transitions of hospital admission, transfer, and discharge, and subsequently comparing it with any newly proposed therapy.[2,3]

Transitions of care are targeted for good reason: Research shows they are critical junctures at which changes in medication occur and, unfortunately, where mistakes are often made.[3] For example:

- A patient may be admitted to the hospital and receive a duplicate prescription, such as a second medication in the same drug class.
- A patient may be moved from the intensive care unit to a general ward, where staff inadvertently omit a prescribed treatment.
- A patient may be discharged home or to a skilled nursing facility with a new medication that interacts with one of his or her nutritional supplements.[2]

The AHRQ says unintended medication changes occur in about one-third of patients who transfer from one hospital unit to another and in 14 percent of discharged patients.[3]

In fact, one of the most common medication errors occurs when there is a failure to reinitiate drug therapy upon discharge, according to AHRQ. For example, anticoagulants are often stopped during hospitalization, but are resumed on an outpatient basis once the patient has been discharged. Cardiovascular, gastrointestinal, and pulmonary medications are common examples that often fall through these "discharge cracks."[3]

Reducing Costs Through Medication Reconciliation

As a tool to reduce costly readmissions, medication reconciliation shows promise. A 2009 study in the *Annals of Internal Medicine* found that a formal medication reconciliation program reduced emergency department use and readmissions within 30 days of discharge by about 30 percent.[4] A nurse advocate helped curb utilization by working with patients to confirm medications, arrange follow-up appointments, and provide educational services. In addition, a pharmacist called patients two to four days after discharge to review medications. Hospital costs were 33 percent lower among patients who received the nurse-pharmacist follow-up, compared with those patients who didn't receive the intervention.[4]

Even when readmissions are not a concern, medication reconciliation can reduce the inappropriate use of costly medications after discharge. A 2010 report in the *Journal of Managed Care Pharmacy* found that inappropriate continuation of proton pump inhibitor therapy during the first 30 days after discharge cost a managed care organization and its members more than $3 million.[5]

Based on these early findings, more managed care organizations are investigating medication reconciliation

30%

A 2009 study in the *Annals of Internal Medicine* found that a formal medication reconciliation program reduced emergency department use and readmissions within 30 days of discharge by about 30 percent.

as a strategy to reduce costs. Organizations such as Harvard Pilgrim Health Care of Wellesley, Mass., and Kaiser Permanente of Aurora, Colo., have investigated medication reconciliation pilot programs.

At Harvard Pilgrim, managed care leaders have adapted hospital-based medication reconciliation models to the outpatient setting. This includes comparing a patient's pre- and post-hospital medications at the time of discharge. In their medication reconciliation process, nurse care managers collect medication information by phone within three days of discharge, and clinical pharmacists check the information against Harvard Pilgrim's pharmacy benefit management database. The clinical team uses an electronic care management application to facilitate communication between nurse care managers and pharmacists. The program costs about $5,000 each year for calls in addition to clinical pharmacist salaries. Medication reviews take about 20 to 30 minutes per patient. But managed care leaders estimate the program could save $1.4 million in avoided hospitalizations for gastrointestinal bleeding due to warfarin misuse alone.[6]

According to a 2008 study in *Pharmacotherapy*, a pilot pharmacist-managed medication reconciliation program at Kaiser decreased mortality by 78 percent after discharge from a skilled nursing facility.[7] However, emergency department visits and readmissions rates were similar between the control and medication reconciliation groups. The authors attributed the decrease in mortality to better identification of potential drug-related problems, including a patient who had been taking dangerously high doses of warfarin after discharge. During a call with the patient, the pharmacist determined that the patient was complying with conflicting instructions. The pharmacist then provided information on the proper dose and arranged for the patient to be evaluated in the clinic.[7]

Creating Effective Interventions

When designing medication reconciliation programs, payers and providers may choose to focus on those patient populations at high risk for repeated readmissions. According to the aforementioned *New England Journal of Medicine* study that examined readmissions among Medicare beneficiaries, the patient populations most likely to be rehospitalized within 30 days were those originally treated for heart failure, pneumonia, chronic obstructive pulmonary disease (COPD), psychoses, and digestive problems.[1]

Among surgical patients, those most likely to be rehospitalized were patients who had cardiac stent placement, major hip or knee surgery, vascular surgery, major bowel surgery, and other orthopedic procedures.[1]

The types of medication reconciliation processes described in the medical literature are varied. Some methods involve staff utilization of a standardized medication form, such as those available from the Institute for Healthcare Improvement or the Joint Commission.[4] Digital tools are also gaining ground. An electronic medication reconciliation application tool helped reduce unintentional medication discrepancies with potential for harm by 28 percent, according to a 2009 study published in the *Archives of Internal Medicine*.[8]

Some medication reconciliation programs rely upon a hospital's computerized provider order entry (CPOE) system. For example, a doctor or nurse enters the patient's prescriptions into the CPOE system upon admission. During the hospital stay, a pharmacist checks the prescriptions for dosage, duplication, interactions, and contraindications. At discharge, the staff prints a list of medications with instructions and reviews necessary self-care steps with the patient. Staff also may instruct the patient to share this list with his or her primary care provider for seamless continuity of care.[9]

Potential Obstacles for Medication Reconciliation

While reducing rehospitalizations due to drug errors is an important objective, there are challenges facing both payers and providers. The AHRQ says mounting time constraints and increasing workloads experienced by providers are often cited as barriers to their consistent provision of comprehensive care.[3] Health plans also share time and staff constraints, as well as the challenge of following up with patients at various stages along the continuum of care. A medication reconciliation process may initially take 30 to 60 minutes per admission, according to AHRQ. However, a standardized reconciliation process may help reduce the overall workload of busy hospital staff by saving time and creating efficiencies that are enjoyed farther downstream in the care cycle. Some research shows reconciliation can reduce nursing time by 20 minutes and pharmacy time by 40 minutes at the time of transfer.[3]

Another potential obstacle is that the very concept of medication reconciliation is still relatively nascent. While the financial benefits look promising, the studies are limited. For example, not all research has shown that medication

reconciliation can prevent rehospitalizations.[3] A study in the *Archives of Internal Medicine* found medication reconciliation had no effect on readmission rates at 14 or 30 days after discharge, nor were emergency department visits reduced.[10] However, the intervention did improve quality by identifying and reconciling medication discrepancies at discharge. The mixed results could be due to variations in medication reconciliation processes, patient education, and timeframe for readmission.[10]

Evidence that medication reconciliation can improve clinical outcomes is also somewhat limited, and agencies like the AHRQ are calling for more research. Others are looking for better-designed studies that test different strategies for reconciling medications. For now, payers and providers will have to view medication reconciliation as a promising tool for reducing healthcare costs.

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Why Hospitals Are Motivated to Reduce Readmissions: Reimbursement and Accreditation

Payers already have an incentive to avoid costly readmissions. It could be argued, though, that hospitals have had little reason to curb readmissions, which have been a source of revenue. But that's changing.

Under the new Affordable Care Act, government payments will increasingly be linked to quality measures, including readmissions rates. If medication reconciliation can improve quality measures, hospitals could stand to gain under CMS' new value-based purchasing program. Under the program, hospitals that perform well on quality measures will receive higher payments beginning in FY 2013 for inpatient discharges occurring on or after October 1, 2012. Part of the Affordable Care Act, the program applies to hospital stays under the Inpatient Prospective Payment System (IPPS).[11]

Another reason hospitals may be more willing to partner with payers is that reconciling medications across the continuum of care is once again a Joint Commission patient safety goal. In 2009, the Joint Commission stopped formal scoring for medication reconciliation as part of its accreditation process,[2] but the agency has issued new guidelines on medication reconciliation, effective July 1, 2011.[12, 13]

High-Stakes Policy for Medicare Health Plans: Navigating Through the Star Ratings

Mona M. Chitre, PharmD, CGP, Director, Clinical Services, Strategy and Policy, FLRx Pharmacy Management, Excellus BlueCross BlueShield

Star ratings aren't only used to evaluate and rank movies, restaurants, consumer products, and hotels—they also rank Medicare Advantage Plans.

The Centers for Medicare and Medicaid Services (CMS) have implemented a 5-star quality rating program to monitor the quality and performance of Medicare Advantage Plans.

"The 5-star rating system helps people with Medicare make meaningful distinctions between high-performing and low-performing health plans," said CMS Administrator Donald M. Berwick, MD. "They also allow plan sponsors to see how they compare to other plans, and encourage them to improve care and customer service so that their plans are more attractive to Medicare beneficiaries."

With the high-stake policy changes that occurred in the spring of 2010, CMS star ratings have large financial implications. Medicare Advantage Plans that earn the highest performance rating—5-stars, or "excellent" performance—are eligible to receive the largest bonuses, equal to 5 percent. In 2012, Medicare Advantage Plans that have a rating of three stars and higher will qualify for a bonus payment.[1] It is estimated that if the bonus plan had been in effect in 2009, top-rated plans would have been awarded nearly $13 billion in bonuses payments.

What Are Star Ratings?

Medicare Advantage Plans receive an overall score for the quality of their services, spanning 36 different topics in five categories:

- Staying healthy
- Managing chronic conditions
- Ratings of health plan responsiveness and care
- Health plan member complaints and appeals
- Health plan telephone customer service.

For plans covering drug services, the overall quality score for those plans covers 17 different topics in four categories:

- Drug plan customer service

Mona M. Chitre, PharmD

- Drug plan member complaints and Medicare audit findings
- Member experience with drug plan
- Drug pricing and patient safety: This includes how well the plan prices prescriptions and how often members with certain medical conditions get prescription drugs that are considered safer and clinically recommended for their condition.

For Medicare Advantage Plans that cover both health and drug services, the overall quality score covers all of the 53 topics listed. Star ratings are determined from plan data including Medicare HEDIS scores, the Health of Seniors (HOS) survey, CAHPS survey score, and plan performance data.

How Do the Star Ratings Impact the MA Business?

Until recently, the star ratings were intended to allow consumers to easily differentiate between plans with the ability to do side-by-side comparisons using the Medicare Plan Finder tool and locate all available MA plans in their area. The star ratings drastically changed in the spring of 2010, when Congress mandated that CMS use star ratings to make quality bonus payments to higher-rated plans.[2] The 2011 ratings released in November 2010 serve as the basis for a quality bonus payment in the demonstration for MA plans in contract year 2012. The demonstration expands on the quality bonus payments authorized in the Affordable Care Act by providing stronger incentives for plans to improve their performance, thus accelerating quality improvements.[1]

Starting in 2012, plans with a minimum 4-star rating can achieve a 1.5 percent bonus. Additionally, plans in qualifying counties have an opportunity to receive a double bonus. Qualifying counties have 25 percent or more MA penetration, received the urban floor payment in 2004, and have a FFS rate lower than the national FFS per capita rate. Examples of qualifying counties include Albany, N.Y., Albuquerque, N.M., and Portland, Ore. In 2014, high-performing plans in these markets can receive a quality bonus as high as 10 percent.[3]

High-performing plans will also get favorable treatment in rebates from CMS that are used to provide additional benefits or reduced costs under the competitive bidding process. Under the new approach, a plan with a very good performance star rating (4.5) will get a 70 percent rebate, while a plan with an average performance star rating (3) will only receive a 50 percent rebate.[3]

Other Perks for Top-Rated Plans

Beginning in 2012, in addition to receiving enhanced rebates and higher bonus payments, 5-star plans will also have the opportunity to enroll members in a Special Election Period (SEP).

- CMS announced on November 19, 2010, that 5-star MA plans can enroll Medicare-eligible beneficiaries at any point during the year.
- Beneficiaries that are eligible for this SEP are 1) enrolled in MA plans with star ratings of 4.5 or less and 2) enrolled in original Medicare and meet eligibility requirements for Medicare Advantage.
- Medicare Advantage Plans receiving 4.5 stars or lower will not only be competing for members against 5-star plans in the same service area, but could potentially experience increased rates of disenrollment as high-performing plans can enroll Medicare-eligible beneficiaries at any point during the year with the addition of an SEP. Higher-performing MA plans have a significant advantage over lower-performing plans and will certainly gain more market share as a result.

Additional Changes to the Star Ratings in 2010

In addition to incentivizing MA plans with bonus opportunities and an SEP, other significant changes that CMS implemented to the star ratings include:

- The addition of detailed measures around diabetes care and cholesterol screening, and an "overall" score for MA-PD plans that averages the 51 health and drug plan measures. (Three complaint measures are duplicative in both health and drug plans.)
- A "low-performer" icon ( ): Plans with fewer than three stars consistently over the prior three years will be flagged as low-quality on the Medicare Plan Finder tool on the Medicare website (www.medicare.gov). The low-performer icon will appear on 5 percent of contracts (28 out of 523 contracts), which cover approximately 7 percent of enrollees, in 2011.[6]

Which Health Plans Have Received Excellent Quality Ratings?

In 2011, three health plans (out of 523 contracts nationwide) received an overall rating of excellent performance or 5-stars. The following contracts are all Health Maintenance Organizations (HMOs), operated by non-profit organizations. They are:

- Capital Health Plan in northern Florida (owned by Blue Cross Blue Shield of Florida)
- Security Health Plan of Wisconsin (owned by the Marshfield Clinic)
- Kaiser Permanente's Senior Advantage, which operates in Colorado and parts of Arizona.[6]

> **"You are going to have to continue to innovate and improve operations ... The business is changing in a fundamental way."**
> *— Frank Ingari, CEO of Essence Healthcare*

According to the Chief Administrative Officer of Security Health Plan, Steve Yuso, the plan has received a 5-star rating as a result of their efforts to manage members' health by working closely with providers and members. Security Health Plan utilizes mailings and personal phone calls to remind members about any needed care and assist in maintaining optimal health. To ensure that members have all the resources needed to recuperate from an illness or injury, the plan provides them with nurse visits at home or in the hospital to review any medication or ongoing care inquiries members may have.

Despite average Prescription Drug Plan (PDP) ratings for Medicare Advantage Plans decreasing from 3.59 stars in 2009 to 3.38 stars in 2011,[6] there are five PDPs (out of 350 contracts) that have received a 5-star rating or "excellent" performance from CMS. They are MedicareBlue Rx, offered by Wellmark Blue Cross and Blue Shield; MedicareBlue Rx, offered by Blue Cross and Blue Shield of Nebraska; Medco Medicare Prescription Drug Plan, offered by Medco Health Solutions; Rx 1 and Rx 3, offered by Excellus Blue Cross Blue Shield; and Medicare Prescription Drug Plan, offered by EmblemHealth.

For Excellus Blue Cross Blue Shield in Rochester, N.Y., the success of its 5-star plan is attributed to creating best-practice Medication Therapy Management (MTM) programs that deliver clinical and economic benefits to providers, members, and plan sponsors. The plan's MTM programs have been instrumental in the decrease of medication error and the improvement of outcomes through adherence in their most vulnerable population—Medicare members.

Members are educated about their conditions through targeted mailings related to drug interactions and medication safety. Members also receive cost-saving tips. Recently, more than 1,800 members were targeted via direct mail if they were on amitryptyline (a drug listed as inappropriate in the elderly due to risk of falls, dizziness, and drowsiness). Providers also received a tip sheet on drug conversion opportunities. Forty-four percent of member discontinued amitryptyline after the plan's intervention, resulting in an estimated savings of $250,000.

1,900 members were also targeted via mail if they had two or more opportunities to transition to generic drugs.[8] A generic drug is approved by the Food and Drug Administration (FDA) as having the same active ingredients as the brand-name drug. Generally, generic drugs cost less than brand-name drugs. Fifteen percent of patients who received the mailing converted to generic drug prescriptions, resulting in a savings of more than $600,000, in addition to improved patient affordability and adherence.[8]

The SafeRx® program, the plan's MTM program, provides eligible members who will be on at least eight chronic medications and have two chronic conditions (hypertension, osteoporosis, coronary heart disease, diabetes, congestive heart failure, or high cholesterol) and have an annual drug spend of at least $3,000 with a personal consultation with a clinical pharmacist. The one-on-one customized pharmacist consult represents the company's integrated and patient-centric approach. An action plan and recommendation are provided to the patient as well as the provider.[8]

Member satisfaction and prescription drug safety (both are variables factored into star ratings) are incredibility important to the plan, as they have implemented an "Ask the Pharmacist" mailbox. The mailbox is hosted on a secure, encrypted

e-form on the web that is monitored daily by a health plan clinical pharmacist. The plan has seen a 700 percent increase in the volume of questions received from 2009 to 2010.[8] The plan has also seen an overall increase of enrollment from 2010 to 2011 of 21 percent.[8]

How Do Star Ratings Impact MA Beneficiary Buying Decisions?

According to the Kaiser Family Foundation, 62 percent of MA plans received star ratings and 86 percent of MA members were in rated plans.[6] While the current number of Medicare beneficiaries enrolled in a plan receiving four or more stars is around 24 percent,[6] this number will undoubtedly increase in 2012 as plans compete based on quality and performance, and no longer solely on price.

Sixty percent of Medicare Advantage enrollees are covered by contracts with scores of 3.5–3.0, which CMS would define as an average performance, and 7 percent of enrollees are in contracts that received ratings that were below average, or "poor" performance.[6] For 2011, the average overall rating is 3.47 stars, weighted by 2010 plan enrollment. Nearly 24 percent of contracts were not rated by the CMS in 2011.[6]

"It is imperative for plans to recognize that we have to shift strategic focus away from sales and marketing," says John Gorman, CEO of the Gorman Health Group. "That is where you put your energy when you get double-digit reimbursement increases, but that party is over. Now the focus shifts to chronic care management, getting back to some new basics on how you aggressively manage seniors with multiple comorbidities. Washington is now saying very clearly that if you can't bend the curve with these folks, then you might as well put up your cleats and go home."

The stakes are high in today's new regulatory climate, and health plans can't afford to leave money on the table. Top-rated MA plans will have the luxury of receiving bonus payments in addition to enhanced rebates and the opportunity to take advantage of a Special Election Period (SEP), enrolling eligible beneficiaries throughout the year. Top plans will be the survivors. According to Frank Ingari, CEO of Seattle-based Essence Healthcare, "The next five years are going to see declining reimbursements and escalating costs. It is a Darwinian situation, and the survivors are going to be the ones who master that learning curve. You are going to have to continue to innovate and improve operations. The game is changing. The business is changing in a fundamental way."[10]

In order to master the learning curve and keep up with the volatile regulatory environment, it's imperative that MA plans make quality improvement programs a priority, as well as customer service, medical management programs, chronic disease management, and patient outcomes. High-performing plans that received a 5-star rating in 2011 were able to do so by excelling in the following areas:

- Offering excellent provider relationships to ensure a vast provider network
- Increasing customer service touch points
- Making medical management a priority
- Focusing on the beneficiary and identifying beneficiaries with chronic illnesses
- Improving the clinical care and support beneficiaries with chronic illnesses receive in order to achieve best outcomes.[3]

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PIPELINE TRENDS

NEW DRUG APPROVALS

CARDIOLOGY

Pradaxa™ (dabigatran etexilate)
AWP: $4.05/capsule
WAC: $3.375/capsule
Approved: October 19, 2010
Formulation: capsule
Manufacturer: Boehringer Ingelheim Pharmaceuticals, Inc.
Indication: Pradaxa™ (dabigatran etexilate) is a direct thrombin inhibitor approved for the prevention of thromboembolism in patients with atrial fibrillation.

PSYCHIATRY/PSYCHOLOGY

Latuda™ (lurasidone)
AWP: $16.80/tablet
WAC: $14.00/tablet
Approved: October 28, 2010
Formulation: tablet
Manufacturer: Sunovion Pharmaceuticals, Inc.
Indication: Latuda™ (lurasidone) is an atypical antipsychotic indicated for the treatment of schizophrenia.

INFECTIOUS DISEASE

Natroba™ (spinosad)
AWP: $238.80/1 bottle
WAC: $199.00/1 bottle
Approved: January 18, 2011
Formulation: topical suspension
Manufacturer: ParaPRO, LLC
Indication: Natroba™ (spinosad) is a pediculicide indicated for the topical treatment of head lice infestations.

PSYCHIATRY/PSYCHOLOGY

Viibryd™ (vilazodone)
AWP: TBA
WAC: TBA
Approved: January 21, 2011
Formulation: tablet
Manufacturer: Clinical Data, Inc.
Indication: Viibryd™ (vilazodone) is a dual-acting potent and selective serotonin reuptake inhibitor and a 5-HT1A receptor partial agonist indicated for the treatment of major depressive disorder.

NEW FDA APPROVED INDICATIONS

Drug Name	Approved	New Indication
Cymbalta® (duloxetine)	November 4, 2010	Chronic musculoskeletal pain
Vivitrol® (naltrexone extended-release)	October 12, 2010	Treatment of opioid-dependent patients
Vyvanse® (lisdexamfetamine dimesylate)	November 10, 2010	Treatment of ADHD in adolescents (ages 13-17)

NEW FORMULATIONS AND DOSAGE FORMS

Drug Name	Manufacturer	Approved	Pricing	Advertised Advantage
Abstral® (fentanyl) sublingual tablet (CII)	ProStrakan, Inc.	January 7, 2011	**AWP:** $16.80/tablet 100mcg $19.20/tablet 200mcg $22.80/tablet 300mcg $28.80/tablet 400mcg $38.40/tablet 600mcg $48.00/tablet 800mcg **WAC:** $14.00/tablet 100mcg $16.00/tablet 200mcg $19.00/tablet 300mcg $24.00/tablet 400mcg $32.00/tablet 600mcg $40.00/tablet 800mcg	A sublingual tablet formulation of fentanyl indicated for the management of breakthrough pain in cancer patients tolerant to current opioid therapy
Amturnide™ (aliskiren/amlodipine/hydrochlorothiazide) 150mg-5mg-12.5mg, 300mg-10mg-12.5mg, 300mg-10mg-25mg, 300mg-5mg-12.5mg, 300mg-5mg-25mg tablets	Novartis	December 21, 2010	**AWP:** $2.98/tablet (strength 150mg-5mg-12.5mg) $3.76/tablet (all other strengths) **WAC:** $2.48/tablet (strength 150mg-5mg-12.5mg) $3.13/tablet (all other strengths)	A three-drug combination tablet for the treatment of hypertension to aid in a patient's increased compliance.
Atelvia™ (risedronate sodium) 35mg delayed-release tablets	Warner Chilcott Inc.	October 8, 2010	**AWP:** $30.44/tablet **WAC:** $25.37/tablet	Indicated for the treatment of postmenopausal osteoporosis. The delayed-release formulation allows patients to take this once-weekly bisphosphonate immediately after breakfast, eliminating the need to wait.
Axiron® (testosterone) 30mg/actuation topical solution (CIII)	Eli Lilly and Co.	November 23, 2010	**AWP:** TBA **WAC:** TBA	Available as a pump bottle, Axiron® provides a new alternative dosage form compared to other existing testosterone products.
Bromday™ (bromfenac sodium) 0.09% ophthalmic solution	Ista Pharmaceuticals	October 16, 2010	**AWP:** $155.00/1 bottle **WAC:** $124.00/1 bottle	Once-daily formulation of NSAID bromfenac indicated for the treatment of postoperative inflammation and reduction of ocular pain for patients who have undergone cataract surgery.

The Pipeline Trends information is current as of February 2011. Estimated information (dates, etc.) are subject to change according to additional indications, patents, patent litigation, etc.
Information available from www.fda.gov and pricerx.medispan.com.

NEW FORMULATIONS AND DOSAGE FORMS *continued*

Drug Name	Manufacturer	Approved	Pricing	Advertised Advantage
Fortesta™ (testosterone) 10mg/actuation transdermal gel (CIII)	Endo Pharmaceuticals Inc.	December 29, 2010	**AWP:** $5.01/actuation **WAC:** $4.18/actuation	Available as a pump bottle, Fortesta™ provides a new strength compared to other available testosterone transdermal gels.
Gralise™ (gabapentin) 300mg and 600mg extended-release tablets	Depomed, Inc.	January 28, 2011	**AWP:** TBA **WAC:** TBA	Once-a-day treatment for post-herpetic neuralgia.
Kombiglyze™ XR (saxagliptin/metformin extended release) 2.5mg-1000mg, 5mg-500mg, 5mg-1000mg extended-release tablets	Bristol-Myers Squibb Co. and AstraZeneca	November 5, 2010	**AWP:** $3.67/tablet (strength 2.5mg-1000mg) $7.34/tablet (strengths 5mg-500mg & 5mg-1000mg) **WAC:** $3.05/tablet (strength 2.5mg-1000mg) $6.11/tablet (strengths 5mg-500mg & 5mg-1000mg)	A once-daily, extended-release tablet that combines Onglyza® and metformin extended-release tablets. Kombiglyze™ XR is indicated for the treatment for adults with Type 2 Diabetes Mellitus as an adjunct to diet and exercise to improve glycemic control.
Moxeza™ (moxifloxacin) 0.5% ophthalmic solution	Alcon Laboratories, Inc.	November 19, 2010	**AWP:** $30.58/1 bottle **WAC:** $25.48/1 bottle	Indicated to be used twice a day, this is a decrease in prescribing frequency required compared to the other moxifloxacin ophthalmic solution available, Vigamox®.
Nuedexta™ (dextromethorphan and quinidine) 20mg-10mg capsule	Avanir Pharmaceuticals	October 29, 2010	**AWP:** $9.78/capsule **WAC:** $8.15/capsule	This is a first-in-class dual-action glutamate inhibitor indicated for the treatment of pseudobulbar affect (PBA).

PRICE COMPARISON: ATELVIA™ VS. ACTONEL®	WAC Pricing		Price Difference to Actonel®
	Per Unit	Per Month	
Atelvia™ (risedronate sodium) 35mg delayed release tablet	$25.37	$101.48	0%
Actonel® (risedronate sodium) 35mg tablet	$25.37	$101.48	N/A

PRICE COMPARISON: SUBOXONE® SUBLINGUAL FILM VS. SUBOXONE® SUBLINGUAL TABLET	WAC Per Unit	Price Difference to Suboxone® Sublingual Tablet
Suboxone® Sublingual Film 8mg-2mg	$6.03	-10%
Suboxone® Sublingual Tablet 8mg-2mg	$6.64	N/A

NOW AVAILABLE OVER-THE-COUNTER

As of March 4, 2011, Allegra® is now available over-the-counter from manufacturer Sanofi-Aventis U.S. All Allegra® products are available OTC including both the 12-hour tablets, 24-hour tablets, children's liquid, orally disintegrating tablets, as well as the Allegra-D® 12-hour and 24-hour formulations. Allegra® has been a top-grossing prescription antihistamine over the years and is the most prescribed antihistamine in the United States. Although Allegra® is sold generically (fexofenadine) as a prescription, there is no knowledge at this time if there will be a generic available over-the-counter in the near future.

NEW FIRST-TIME GENERIC DRUG APPROVALS

Donepezil tablets (Aricept®)^
Launched: December 17, 2010

Donepezil orally disintegrating tablets (Aricept® ODT)
Launched: November 29, 2010

Doxycycline hyclate delayed-release 75mg, 100mg tablets (Doryx®)
Launched: December 30, 2010
Note: Not all strengths are available in generic formulation.

Dutasteride capsules (Avodart®)
Approved: December 21, 2010
Launched: TBA

Levocetirizine tablets (Xyzal®)
Launched: November 29, 2010

Levofloxacin 0.5% ophthalmic solution (Quixin®)
Launched: December 20, 2010

Propafenone HCl extended-release capsules (Rythmol® SR)*
Launched: January 3, 2011

Zafirlukast tablets (Accolate®)
Launched: November 19, 2010

Zolpidem extended-release tablets (Ambien® CR)
Launched: October 18, 2010 (6.25mg)‡
December 6, 2010 (12.5mg)•

^ Ranbaxy Laboratories, Inc. has 180-day exclusivity.
* Par Pharmaceuticals has 180-day exclusivity.
‡ Actavis Group has 180-day exclusivity.
• Anchen Pharmaceuticals, Inc. has 180-day exclusivity.

PROJECTED FIRST-TIME GENERIC ENTRY

Latanoprost (Xalatan®)
March 2011

Exemestane (Aromasin®)
April 2011

Letrozole (Femara®)
April 2011

Levofloxacin (Levaquin®)
June 2011

Triamcinolone nasal spray (Nasacort AQ®)
June 2011

Alfuzosin extended-release tablet (Uroxatral®)
July 2011

MEDICATION SPOTLIGHT

Mometasone furoate/ formoterol fumarate (Dulera®*)

**Dulera is a registered trademark of Schering Corporation, a subsidiary of Merck & Co., Inc.*

Background

Asthma is a complex disorder that affects upward of 17.5 million adults in the United States alone.[1] Asthma management focuses on obtaining adequate disease control, which is accomplished through stepwise treatment approaches that vary according to the classification of disease severity. It is important to take a highly individualized approach to treatment, as extensive inter-patient variability can substantially influence therapeutic response and affect the level of control that can be achieved with certain regimens. As new treatments enter the marketplace, asthma patients and their providers are offered new options to enhance their likelihood of obtaining optimal disease control.[1, 5]

Mometasone furoate/formoterol fumarate (Dulera®) is a combination product containing the inhaled corticosteroid (ICS), mometasone (Asmanex®, Schering Corp./Merck), and long acting beta-2-agonist (LABA) formoterol (Foradil®, Astellas Pharma).[2] Since gaining FDA approval in June 2010, mometasone/formoterol has entered a growing asthma management market, joining the likes of fluticasone/salmeterol (Advair®, GlaxoSmithKline), and budesonide/formoterol (Symbicort®, AstraZeneca).[2, 3, 4]

Indications, Dosing, and Warnings/Precautions

Mometasone/formoterol is indicated for the long-term maintenance treatment of asthma in patients ≥ 12 years old who have failed to achieve adequate disease control with inhaled corticosteroid monotherapy (see Table 1 for currently available dosage forms/strengths, and Table 2 for recommended dosing).[2] Like the other LABA/ICS combination products currently approved in the United States, mometasone/formoterol is considered a second-line agent in the treatment of asthma. According to expert treatment guidelines issued by the National Heart, Lung, and Blood Institute, inhaled corticosteroids are the drugs of choice for initial asthma therapy in all age groups with persistent asthma.[5]

Unlike the stand-alone formulations of its individual constituents, mometasone/formoterol is available as a pressurized metered dose inhaler (MDI). For those patients who have difficulty using a pressurized MDI, mometasone/formoterol remains a therapeutically appropriate option, as it is compatible with most commercially available spacers used to improve patient technique and enhance drug delivery into the lungs.[2]

Table 1

Dosage Forms/ Strengths[2]	Delivered Dose of Mometasone Furoate per Actuation	Delivered Dose of Formoterol Fumarate per Actuation
Dulera® (mometasone/ formoterol) 100mcg/5mcg Pressurized MDI	100 mcg	5 mcg
Dulera® (mometasone/ formoterol) 200mcg/5mcg Pressurized MDI	200 mcg	5 mcg

Table 2 RECOMMENDED DOSAGES[2]

Previous Therapy	Recommended Dose	Maximum Recommended Daily Dose
Inhaled medium dose corticosteroids	Dulera® (mometasone/formoterol) 100mcg/5mcg, 2 inhalations twice daily	400mcg/20mcg
Inhaled high dose corticosteroids	Dulera® (mometasone/formoterol) 200mcg/5mcg, 2 inhalations twice a day	800mcg/20mcg

Mometasone/formoterol is not indicated for the relief of acute bronchospasm, and carries a boxed warning for risk of asthma-related death with use of formoterol. It is contraindicated in the primary treatment of status asthmaticus or other acute episodes requiring intensive care, as well as for patients with a known hypersensitivity to any of its components. All warnings and precautions pertaining to the use of the individual components of the formulation, such as immunosuppression due to ICS use or risk of hypokalemia with LABA use, also apply to the combination product. See Table 3 for summarized product description.[2]

Clinical Studies

Two significant pre-marketing studies have demonstrated the efficacy of combination mometasone furoate/formoterol fumarate in the treatment of persistent asthma patients. In these studies, the efficacy of mometasone/formoterol was compared to that of its separate components, mometasone and formoterol, and placebo.[6,7] In both trials, patients on mometasone/formoterol exhibited significant increases from baseline in mean FEV_1 AUC (0-12 hr). In addition, patients on mometasone/formoterol experienced fewer events than those on mometasone, formoterol, or placebo. Overall, both trials have shown the efficacy of mometasone/formoterol in the treatment of persistent asthma in comparison to stand-alone ICS mometasone, stand alone LABA formoterol, or placebo. Combination mometasone/formoterol offers an overall improvement in FEV_1 than either component alone, making it a viable option for patients in need of improved asthma control.[6,7]

Table 3 MOMETASONE/FORMOTEROL (DULERA®)[2]

Indications	• Asthma (patients >12 years old)
Available strengths	• Mometasone/formoterol 100mcg/5mcg • Mometasone/formoterol 200mcg/5mcg
Contraindications	• Status asthmaticus, hypersensitivity
Adverse reactions	• Candida albicans • Cardiovascular events • Headache • Nasopharyngitis • Sinusitis • Uticaria • Wheezing
Warnings/ precautions	• Angina • Asthma-related death* • Cardiovascular and CNS effects • Diabetes mellitus • Drug interactions with strong CYP450 3A4 inhibitors • Growth inhibition • Glaucoma and cataracts • Hyperglycemia • Hypersensitivity • Hyperthyroidism • Hypokalemia • Hypercorticism and adrenal suppression • Immunosuppression • Ketoacidosis • Paradoxical bronchospasm and upper airways symptoms • Reduction in bone mineral density • Seizures
Pregnancy	Category C
Breast Feeding	Unknown; has not been adequately studied
Monitoring Parameters	• Blood glucose • Growth rate • PFTs • Serum potassium
*Indicates boxed warning	

Pricing

Mometasone/formoterol is priced competitively to the other ICS/LABA combinations currently on the market (see Table 4 below).[8]

Considerations for Payers

Mometasone/formoterol is the first combination product containing the ICS mometasone, and offers a new option for those patients who currently use mometasone alone and require a step up in therapy to gain control of their asthma. Prior to the approval of mometasone/formoterol, patients needing a step up in therapy were faced with the burden of either using two separate inhalers and thus increasing their out-of-pocket costs or switching to a combination product containing an alternative ICS.[2] Neither of these options is ideal, as they increase regimen complexity, create potential for patient confusion, and may negatively impact medication adherence.[5]

Despite advances in diagnosis and treatment, adequate control of asthma remains a major challenge. Inhaled corticosteroids remain the gold standard for treatment of persistent asthma, but many patients eventually require a step up in therapy to achieve control of their disease.[5] Unfortunately, the lack of studies that examine the comparative effectiveness of varying ICS/LABA combinations may compound difficulties for physicians and payers in determining which therapies are best utilized for step-up care. Thus, the availability of multiple therapeutic options for use in asthma treatment is vital to enhancing the likelihood of favorable treatment outcomes and minimizing obstacles presented by medication nonadherence.[5] When considering therapy for patients with persistent asthma, mometasone/formoterol stands as a viable option. With competitive pricing and proven efficacy, there seems to be little reason to restrict the availability of mometasone/formoterol for patients requiring an improvement in disease control. Asthma treatment must be tailored to each individual, and increasing access to new therapies may improve the ability of patients to achieve and maintain control of their asthma.[2, 5, 6, 7]

Table 4 — CURRENT PRICING FOR ICS/LABA COMBINATION PRODUCTS[8]

Drug Name	Strength (mcg)	AWP/Month	WAC/Month
Budesonide/formoterol (Symbicort®, AstraZeneca)	80/4.5	$212.00	$176.67
	160/4.5	$242.32	$201.93
Fluticasone/salmeterol (Advair® Diskus®, GSK)	100/50	$204.65	$170.54
	250/50	$254.27	$211.89
	500/50	$334.45	$278.71
Fluticasone/salmeterol (Advair® HFA, GSK)	45/21	$204.65	$170.54
	115/21	$254.27	$211.89
	230/21	$334.45	$278.71
Mometasone/formoterol (Dulera®)	100/5	$225.72	$188.10
	200/5	$225.72	$188.10

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1. United States. Centers for Disease Control and Prevention. Asthma. Oct 2010. URL: **www.cdc.gov/asthma/**.
2. Dulera (mometasone furate; formoterol fumarate inhalation aerosol) package insert. Whitehouse Station, NJ: Schering Corporation; 2010.
3. Symbicort (budesonide; formoterol fumarate dihydrate) inhalation aerosol package insert. Wilmington, DE: AstraZeneca LP; June 2010.
4. Advair (fluticasone; salmeterol) Diskus package insert. Research Triangle Park, NC: GlaxoSmithKline; June 2010.
5. United States. Department of Health and Human Services. National Heart Lung and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Oct. 2007. URL: **www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf.**
6. Nathan RA, Nolte H, Pearlman DS; P04334 Study Investigators. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol fumarate 200/10 microg combination treatment in patietns with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc.* 2010;31(4):269-79.
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8. Price Rx - Login. Feb. 2011. URL: **https://pricerx.medispan.com/Login.aspx.**

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

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

Victoza® made a deep impact in its first year.

- ✓ Over **30,000** health care professionals prescribed Victoza®*
- ✓ 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.

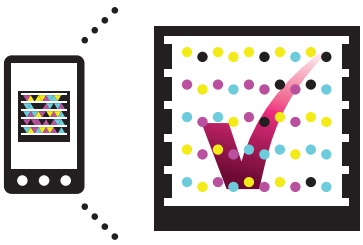
The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated 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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See what patients are saying about Victoza®.
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novo nordisk®

143426 February 2011

VICTOZA®
liraglutide (rDNA origin) injection

Victoza® made a deep impact in its first year.

- ✓ Over **30,000** health care professionals prescribed Victoza®*
- ✓ Over **160,000** patients started taking Victoza®*
- ✓ VictozaCare™ provides patients the support they need to get started

Visit VictozaPro.com or ask your Diabetes Care Specialist for more information.

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.

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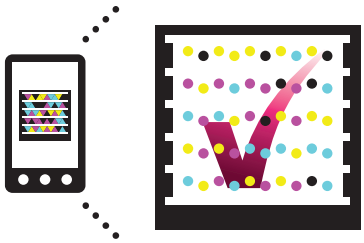

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