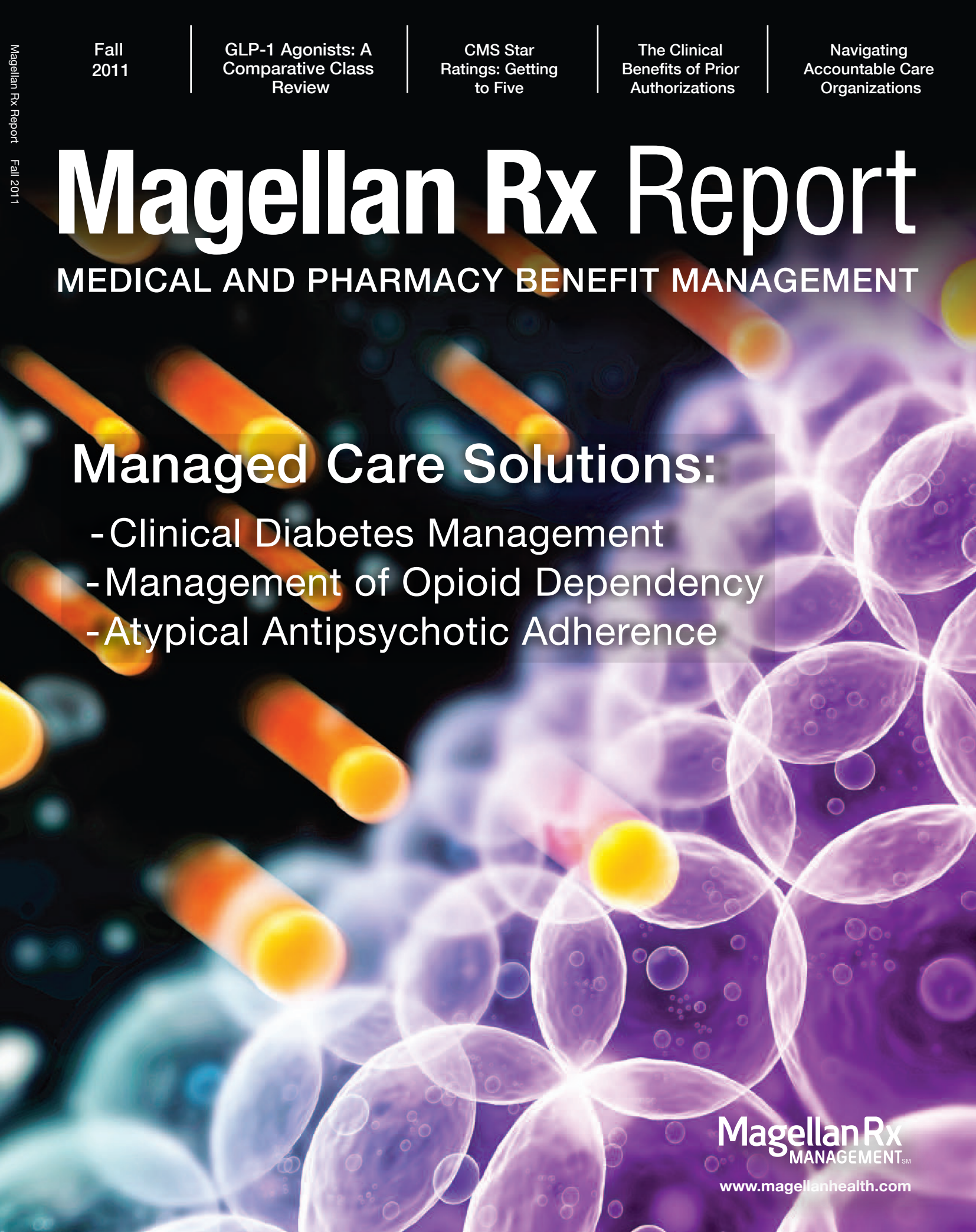
Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT



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- Management of Opioid Dependency
- Atypical Antipsychotic Adherence

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CHRONIC DISEASE MANAGEMENT

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CDMI REPORT

ISSN: 2159-5372

PUBLISHED BY:
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WELCOME

to this issue

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trends

Letter from the President
Susan Petrovas

Dear Managed Care Colleagues,

Susan Petrovas, RPh, President

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

CDMI has developed into the premier chronic disease benefit management company (CDBM) in the country. CDMI manages more than 13 million patient lives, and estimates exceed 20 to 25 million lives by year's end. We support our health plan customers' pharmacy and medical management needs in a wide variety of chronic disease states. Along with our experienced staff of clinical pharmacists and expert analysts, CDMI provides comprehensive and innovative services designed to support our customers in developing and implementing clinical management solutions to effectively meet their chronic disease management needs.

Expanding upon our already stellar clinical offerings are a few new programs that we at CDMI have recently developed and are extremely excited to implement. The first is our Opioid Abuse Management Program. Through a detailed analysis of pharmacy claims data, CDMI can identify those patients who may potentially be abusing/misusing/diverting opioid prescription medication. This inappropriate utilization is associated with a considerable financial impact on the U.S. health system, and managed care is responsible for picking up the bill. Patient identification and comprehensive physician education and outreach have demonstrated substantial cost-saving potential in this patient population.

Another CDMI clinical expansion is designed to assist our customers in improving their HEDIS measures and CMS Star Ratings. The program identifies diabetic patients who are currently not utilizing either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. After performing clinical patient medication assessments, CDMI clinical pharmacists develop therapeutic recommendations for network physicians and develop solutions to appropriately manage patient disease states. This produces an integrated approach to patient care and incorporates clinical pharmacists as essential components of the healthcare team.

For additional information regarding our clinical offerings, or any CDMI services, please feel free to contact me directly at **SPetrovas@CDMIhealth.com**. As always, thanks for reading!

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

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ON THE COVER

The cover art features a detailed illustration of free radicals.

MANAGED CARE NEWSSTAND

Asthma Rates and Costs Continue to Soar

Asthma continues to be a major public health problem in the U.S. From 2001 to 2009, the number of Americans diagnosed with asthma rose by more than 4.3 million. In 2009, about 1 in 12 people received an asthma diagnosis, with all demographic groups experiencing escalating asthma rates. However, the greatest hike—a nearly 50 percent increase—was among black children. A report from the Centers for Disease Control and Prevention (CDC) says the cause of the rising asthma rates is unknown.

Not surprisingly, the costs of asthma also increased during this period. According to the CDC, asthma costs climbed about 6 percent during that span, rising from about $53 billion in 2002 to about $56 billion in 2007. Annual asthma costs averaged $3,300 per patient during this period. A significant number of patients—both uninsured and insured—could not afford their prescription medications.

The report highlights the importance of providing patients with the education and support to control their asthma and curb healthcare costs.

Source: Centers for Disease Control and Prevention. U.S. Asthma Rates Continue to Rise. *Vital Signs*. 2011.

Palliative Care Teams Do More than Ease Patients' Symptoms

Medicaid spends a disproportionate share of funds on patients suffering from serious or life-threatening conditions. A recent study looked at the effect palliative care team consultations have on hospital costs for Medicaid patients at four New York state hospitals. Researchers examined data from 2004 to 2007 and found that the average costs of caring for patients who received palliative care were $6,900 less (per hospital admission) than those incurred by a matched group of patients who received standard care.

$84-$252 MILLION
Estimated annual Medicaid cost savings if hospitals implement palliative care consulting teams

Patients who received palliative care services spent less time in the intensive care unit (ICU), were less likely to die in the ICU, and were more likely to obtain referrals to hospice care than the matched group. Researchers estimated that New York state hospitals could save $84-$252 million in annual Medicaid spending if all hospitals with 150 or more beds had palliative care consulting teams.

Source: Morrison, R. Sean, et al. Palliative Care Consultation Teams Cut Hospital Costs for Medicaid Beneficiaries. *Health Affairs*. 2011;30(3):454-463.

New Tool Predicts Patient Compliance with Prescription Medication

FICO, a company known for creating credit scores, has developed a new score that can help providers customize programs to improve drug adherence, enhance the effectiveness of therapies, and reduce costs. The FICO® Medication Adherence Score uses predictive analytics to calculate the probability that a specific patient will take his or her medications as prescribed.

The technology can create scores for any patient population. It uses publicly available data to develop scores and is compliant with HIPAA regulations. The analytics require little information from patients and do not use sensitive personal health information.

Industry experts estimate that only about half of the 3.2 billion medications prescribed each year are taken as directed—a staggering statistic that has a substantial impact on the healthcare system. A tool that can identify patients' likelihood of complying with prescription medication directions could have a profound impact on patient care. Providers can then design interventions to improve patient outcomes.

Source: FICO. New FICO Analytics Predict Likelihood of Patient Adherence to Prescription Medication. Accessed 14 July 2011 at **www.fico.com/en/Company/News/Pages/06-23-2011a.aspx.**

Substantial Cost Savings Possible with Six-Day Insulin Expiration

As diabetes costs continue to skyrocket in the U.S., researchers modeled the impact of one possible cost-saving opportunity on a hypothetical health plan with 1 million members and extrapolated the results to the total U.S population. The goal of the study was to determine if extending the expiration date on insulin used in insulin pumps would produce significant financial savings.

Specifically, they looked at the impact of lengthening the insulin expiration date from two days to six days—a change already in place for insulin aspart [rDNA origin] (NovoLog®)—when used in certain pumps with improved reservoir stability. One hypothetical group discarded the entire insulin infusion kit every two days, the current recommended practice. The second group changed the needle and cannula on the third day and disposed of the entire infusion kit on the sixth day. The researchers calculated the costs of the discarded insulin and pump components for each group and found that the six-day scenario resulted in annual cost savings of more than $2,800 per patient and $3.4 million per hypothetical health plan. The researchers estimated a national cost savings of more than $1 billion per year.

According to the researchers, using insulin pumps that allow for an expiration date of six days could simplify treatment and cut costs.

Source: Weiss, Richard C, et al. Economic Benefits of Improved Insulin Stability in Insulin Pumps. *Managed Care*. 2011;20(5):42-7.

Preventing Diabetes Is Cost-Effective

Interventions to prevent diabetes in high-risk patients may result in large benefits. One study compared preventive treatment with the medication metformin, lifestyle intervention, and a placebo for a 10-year period. Researchers found that both medication and lifestyle interventions reduced medical costs by $1,700 and $2,600 per person, respectively. Some of the reductions noted were lower costs for prescriptions and inpatient and outpatient care.

The analysis, conducted as part of a follow-up to the landmark National Institutes of Health-sponsored Diabetes Prevention Program, found that implementing lifestyle interventions was more costly than either administering medication or the placebo. But the interventions—losing 7 percent of body weight and doing 150 minutes of moderate-intensity exercise per week—were more effective in preventing diabetes and improving patients' quality of life. At the end of 10 years, the risk of developing diabetes was 34 percent lower for those in the intervention group and 18 percent lower for those receiving metformin.

The researchers noted that both interventions are cost-effective ways of stemming the rising incidence and costs of diabetes.

Source: Herman, William H, et al. Follow Up Analyses of DPP Show Lifestyle Intervention and Metformin Are Cost-Effective. American Diabetes Association's 71st Scientific Sessions®. 2011.

Adherence to Statins Lowers Healthcare Costs

Patients who take statin medications as prescribed have lower healthcare costs and fewer cardiovascular-related hospitalizations. Researchers completed a retrospective cohort analysis for a one-year baseline period and an 18-month follow-up period. They found that patients who took their statin medications regularly (90 percent or more of the time) incurred $10,162 in healthcare costs during the study period, while those who were noncompliant had $11,106 in medical expenses. The difference in spending was $944 during the 18-month follow-up period. Overall, the adherent group had lower total healthcare costs, with these savings offsetting the increased medication cost.

Statin medications have a proven record of success in lowering low-density lipoprotein (LDL) cholesterol. Unfortunately, more than half of patients have a decline in adherence during the first year of treatment due to high costs, side effects, and lack of symptoms.

The researchers say improving adherence for the millions of patients who are nonadherent to their statins could save an estimated $3 billion in healthcare costs each year.

Source: Pittman, Donald G, et al. Adherence to Statins, Subsequent Healthcare Costs, and Cardiovascular Hospitalizations. *American Journal of Cardiology.* 2011;107(11):1662-6.

Comparative Effectiveness and Managed Care Implications of GLP-1 Agonists in the Treatment of Type 2 Diabetes Mellitus

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David R. Brown, MD, PhD, Endocrinologist

The glucagon-like-peptide-1 (GLP-1) agonists are a class of medications used in the treatment of Type 2 Diabetes Mellitus (T2DM). Exenatide (Byetta®) and liraglutide (Victoza®) are the only GLP-1 agonists currently available in the U.S. (see Table 1). A long-acting release formulation of exenatide (exenatide-LAR; expected to be marketed as Bydureon™) may be approved by the U.S. Food and Drug Administration (FDA) in the near future; it was recently approved in the EU.[1] Until recently, there has been little data available to accurately compare the clinical efficacy and safety of the different GLP-1 agonists. Over the past few years, however, results from several head-to-head trials have been released and published,[2-6] assisting healthcare professionals and managed care organizations in evaluating the relative merits of these different GLP-1 agonists.

TABLE 1. THE GLP-1 AGONISTS

GLP-1 Agonist	Brand Name	Manufacturer	FDA Approval	Dosing Frequency
Exenatide	Byetta®	Amylin/Lilly/ Alkermes	2005	Twice daily
Liraglutide	Victoza®	Novo Nordisk	2010	Once daily
Exenatide-LAR	Bydureon™	Amylin/Lilly/ Alkermes	Pending	Once weekly

Background

After demonstrating success in improving glycemic control in T2DM patients, exenatide BID was approved by the FDA in 2005, launching the GLP-1 medication class onto the U.S. market.[7] Phase three clinical trials of exenatide focused on placebo-controlled studies and non-inferiority trials against insulin glargine and insulin aspart 70/30. As the inaugural GLP-1 agonist, no head-to-head trials with other GLP-1 agonists were conducted during its developmental phase.

Liraglutide QD was approved by the FDA in 2010.[8] Unlike exenatide, liraglutide trials compared the GLP-1 agonist to a wide range of drugs used to treat diabetes, including the sulfonylureas (SUs), dipeptidyl peptidase-4

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inhibitors (DPP-IVs), thiazolidinediones, and insulin glargine. A head-to-head trial with exenatide was also conducted.

Similar to liraglutide, exenatide-LAR trials consist of head-to-head studies with several other diabetes drug classes,[9] as well as head-to-head comparisons of exenatide BID and liraglutide. Due to several requests from the FDA seeking additional information, exenatide-LAR is still pending approval.[10,11]

Not surprisingly, since they are of the same medication class, these drugs have many similarities. They improve glycemic control, share the same route of administration (subcutaneous injection), have similar indications (exenatide and liraglutide; no U.S. label is available at this time for exenatide-LAR), may promote weight loss, have a low hypoglycemia risk, and may also have cardiovascular benefits. Additionally, their general safety profiles, including common adverse reactions such as gastrointestinal (GI) effects, and warnings and precautions, are largely similar.

Despite these similarities, there are several noteworthy differences between the GLP-1 agonists, even before taking into consideration the results from the head-to-head trials. One important difference is their dosing schedule. Exenatide is dosed twice daily within 60 minutes of meals, while liraglutide is dosed once daily without regard to meals.[7,8] Exenatide-LAR is dosed once weekly, also without regard to meals.[9] Both exenatide and liraglutide are administered using a convenient pen device. Exenatide-LAR, however, is expected to require reconstitution prior to each dose. Also, the anticipated needle size for exenatide-LAR is larger compared with the other GLP-1 agonists.[12] In terms of blood glucose lowering, exenatide primarily targets postprandial glucose with a residual effect on fasting levels. Liraglutide has more noteworthy effects on lowering fasting glucose levels with lingering postprandial effects. Regarding safety, liraglutide has a boxed warning due to the development of thyroid tumors in rodent studies; this effect has not been observed in other animal models or in humans. Thyroid tumors have also been observed in exenatide-exposed rodents, suggesting that this may be a class effect of GLP-1 agonists. However, exenatide does not have a boxed warning on its label, and the label language regarding exenatide-LAR exposure and rodent thyroid tumors is not yet available from the FDA.

Head-To-Head Trials

Several head-to-head GLP-1 agonist trials have been conducted (see Table 2, page 10) utilizing HbA_{1c} reduction as the primary outcome. The LEAD-6 trial was the first of these large late-phase trials to be completed.[2] Participants were randomized to either liraglutide 1.8 mg daily or exenatide 10 mcg BID in addition to their previous therapy of metformin, SU, or both. The 26-week trial resulted in a significant improvement in HbA_{1c} reduction with liraglutide compared with exenatide. Fasting plasma glucose (FPG) reduction, the percentage of patients reaching HbA_{1c} goals of <7 percent and ≤6.5 percent, and patient satisfaction were also significantly greater in the liraglutide treatment group. Postprandial glucose reduction was greater with exenatide after breakfast and dinner, but not after lunch. Weight loss was similar between the two patient groups. The rates of nausea were similar between liraglutide and exenatide during the initiation of treatment, but significantly fewer patients in the liraglutide group experienced nausea at the conclusion of the trial compared with those in the exenatide group. Rates of hypoglycemia were also lower in the liraglutide treatment group. Total adverse events reported and withdrawal rates were similar between the two GLP-1 agonists. A 14-week extension of the LEAD-6 trial was conducted to measure the benefit of switching patients from exenatide to liraglutide.[3] Additional benefits were observed in HbA_{1c} reduction, FPG reduction, the percentage of patients reaching target HbA_{1c} levels, and patient satisfaction.

Two large late-phase trials comparing exenatide and exenatide-LAR have been completed. DURATION-1, the first of these trials, was a 30-week noninferiority trial in which patients were randomized to either exenatide-LAR 2 mg weekly or exenatide 10 mcg twice daily.[4] Patients given exenatide-LAR weekly experienced a significantly greater HbA_{1c} reduction compared with those in the exenatide twice-daily group. FPG reduction and the proportion of patients achieving target HbA_{1c} levels were also significantly greater in the exenatide-LAR group. Weight loss was similar between the two patient groups. The incidence of nausea was significantly less with exenatide-LAR. Injection site pruritus, an adverse effect commonly associ-

TABLE 2. SELECTED RESULTS FROM GLP-1 AGONIST HEAD-TO-HEAD TRIALS

	LEAD-6	DURATION-1	DURATION-5	DURATION-6
GLP-1 agonists studied	Liraglutide 1.8 mg daily vs. Exenatide 10 mcg BID	Exenatide-LAR 2 mg weekly vs. Exenatide 10 mcg BID	Exenatide-LAR 2 mg weekly vs. Exenatide 10 mcg BID	Exenatide-LAR 2 mg weekly vs. Liraglutide 1.8 mg daily
HbA_{1c} at end of trial	7.1% (Liraglutide) vs. 7.3% (Exenatide)	6.4% (Exenatide-LAR) vs. 6.8% (Exenatide)	7.1% (Exenatide-LAR) vs. 7.7% (Exenatide)	Not reported
HbA_{1c} reduction from baseline	-1.12% (Liraglutide) vs. -0.79% (Exenatide)	-1.9% (Exenatide-LAR) vs. -1.5% (Exenatide)	-1.6% (Exenatide-LAR) vs. -0.9% (Exenatide)	-1.5% (Liraglutide) vs. -1.3% (Exenatide-LAR)
Percentage of patients achieving goal HbA_{1c}	<7%: 54% (Liraglutide) vs. 43% (Exenatide) ≤6.5%: 35% vs. 21%	≤7%: 77% (Exenatide-LAR) vs. 61% (Exenatide) ≤6.5%: 49% vs. 42%	<7%: 58.1% (Exenatide-LAR) vs. 30.1% (Exenatide) ≤6.5%: 41.1% vs. 16.3%	<7%: 60.2% (Liraglutide) vs. 52.3% (Exenatide-LAR)
Change in body weight	-3.24 kg (Liraglutide) vs. -2.87 kg (Exenatide)	-3.7 kg (Exenatide-LAR) vs. -3.6 kg (Exenatide)	-2.3 kg (Exenatide-LAR) vs. -1.4 kg (Exenatide)	-3.58 kg (Liraglutide) vs. -2.68 kg (Exenatide-LAR)
Rate of nausea	Overall: 25.5% (Liraglutide) vs. 28% (Exenatide) At 26 wks: 3% vs. 9%	26.4% (Exenatide-LAR) vs. 34.5% (Exenatide)	14% (Exenatide-LAR) vs. 35% (Exenatide)	20% (Liraglutide) vs. 9% (Exenatide-LAR)

ated with long-acting injectables, occurred at a higher incidence with exenatide-LAR. Serious adverse events and withdrawal rates were similar between the two formulations of exenatide. An extension of the DURATION-1 trial was conducted to evaluate the benefit of switching to exenatide-LAR following 30 weeks of treatment with exenatide twice daily.[5] Patients in the exenatide twice-daily group who switched to exenatide-LAR experienced further reduction in HbA_{1c}. An increase in FPG levels was initially observed in these patients, but a rapid decrease soon followed after two weeks of treatment. This was attributed to the time it takes to establish therapeutic levels of exenatide when using the long-acting formulation.

The second exenatide vs. exenatide-LAR head-to-head study was the 24-week DURATION-5 trial.[6] The primary difference between these two trials is that since DURATION-5 occurred later in the developmental phase, the intended commercial product was actually used. Results of DURATION-5 were similar to those of DURATION-1. Exenatide-LAR significantly reduced HbA_{1c} and FPG levels compared with exenatide twice daily. Safety results were also similar to the previous trial; nausea occurred more frequently with exenatide twice daily and injection-site reactions were more common with exenatide-LAR.

The most recently completed head-to-head GLP-1 agonist trial was the 26-week DURATION-6 trial, which compared exenatide-LAR to liraglutide.[13] The resulting HbA_{1c} reduction for patients in the exenatide-LAR group did not meet the criteria for noninferiority to liraglutide (HbA_{1c} reduction of 1.3 percent with exenatide-LAR vs. 1.5 percent with liraglutide). Exenatide-LAR patients experienced less gastrointestinal adverse events compared with liraglutide patients, but injection site nodules occurred more commonly with exenatide-LAR. The percentage of patients completing the study was the same in both groups. Results from the DURATION-6 trial were released in March 2011. More data remains to be evaluated from the trial, and upon completion, is expected to be submitted for publication to a peer-reviewed journal.

Clinical Summary

During the past two years, four major head-to-head trials comparing GLP-1 agonists have been completed (DURATION-6 awaits publication). As a result, considerable information is now available to adequately evaluate this expanding drug class.

Liraglutide was the first GLP-1 agonist to significantly outperform another GLP-1 agonist in a head-to-head trial, as measured by its HbA_{1c} reduction ability relative to exenatide.[2] Exenatide-LAR also significantly outperformed exenatide in clinical trials;[4-6] however, results from the DURATION-6 trial failed to prove exenatide-LAR is noninferior to liraglutide.[13] The once-weekly dosing frequency and its tendency to cause fewer GI side effects are favorable characteristics, but the required reconstitution that complicates its administration may detract from its appeal to patients and providers.

Each GLP-1 agonist has its advantages and disadvantages. Results from head-to-head trials have thus far established liraglutide as the GLP-1 agonist with the strongest ability to improve glycemic control, using HbA_{1c} reduction as the

primary benchmark. Its once-daily dosing frequency is also favorable compared with the twice-daily dosing of exenatide, the other GLP-1 agonist currently available. Patients will need to be informed of the differences between each agent and make a selection with their provider based on which GLP-1 agonist best fits their needs and lifestyle.

Managed Care Implications

When the GLP-1 agonist class first arrived on the diabetes market, managed care organizations and prescribers alike were faced with the decision of how to approach the new drug class. In the diabetes marketplace, which is highly dominated by generic medications, managed care organizations are hesitant to consider new and seemingly expensive agents for preferred formulary status. In addition, many of these organizations fail to appreciate the clinical differentiation of the GLP-1 agonists as a class, as well as the individual benefits offered by the specific agents. However, after reviewing the literature, the clinical benefits of the GLP-1 agonists, such as HbA_{1c} reduction, low hypoglycemia risk, and weight loss, are difficult to dispute. The two currently available GLP-1 agonists each offer unique clinical benefits and should be strongly considered as therapeutic treatment options in the management of T2DM.

When considering formulary placement, cost is an obvious concern for managed care organizations. GLP-1 agonists are not inexpensive, and there are currently no generic formulations available.[14] However, since current guidelines give strong recommendations for the use of GLP-1 agonists in different T2DM patient scenarios,[15,16] the managed care industry will likely be increasingly encouraged to make these medications available to their subscribers. The benefits of GLP-1 agonists as components of individualized treatment regimens that allow patients to achieve superior HbA_{1c} reductions with less weight gain and hypoglycemia will become increasingly apparent to the industry, patients, and providers alike. When reviewing the GLP-1 agonists for formulary placement, the decision-making process must extend far beyond cost considerations and include primary and secondary clinical outcomes, their safety profiles, patient satisfaction, and adherence.

Strictly focusing on the two currently approved GLP-1 agonists, liraglutide appears to have the superior overall clinical profile based on results from the LEAD-6 trial. In addition to greater HbA_{1c} lowering, liraglutide-treated patients benefit from a once-daily dosing schedule. The difference in dosing frequency may influence patient adherence, currently a popular topic throughout the managed care industry.[17] In addition, liraglutide is administered without regard to meals, giving patients greater flexibility and potentially increasing treatment compliance. For payors who place a higher emphasis on clinical efficacy, patient satisfaction, and treatment adherence, liraglutide may be an appropriate choice for formulary addition.

As the first GLP-1 agonist on the market, exenatide has a longer history of real-world utilization. This may be interpreted by some as an advantage. The longer duration of market availability, resulting in greater post-marketing experience, may engender greater confidence in the safety profile. Also, cost is an advantage of exenatide. When comparing the prices of the commonly used doses of each available GLP-1 agonist, exenatide is 25 percent less expensive.[14] Additionally, the manufacturer of exenatide is pursuing an additional indication for the co-administration with long-acting basal insulin. Clinical trials have demonstrated significant HbA_{1c} reductions when exenatide is used in combination with insulin glargine.[18] Considering all the clinical and economic data, it may be a reasonable approach to have both exenatide and liraglutide as co-preferred treatment options on formulary.

It is currently unclear how the entry of exenatide-LAR to the pharmaceutical market will influence the managed care industry's evaluation of the GLP-1 agonist class. Although exenatide-LAR remains unapproved by the FDA, many managed care executives are likely waiting for this product before making any final decisions on how to manage the GLP-1 agonist class, regardless of the clinical advantages offered by liraglutide and exenatide.

The approval process of exenatide-LAR has suffered from multiple delays.[10,11] The New Drug Application (NDA) was first accepted for review by the FDA in July 2009.[19] In March 2010, the FDA requested more information regarding product labeling, REMS, and the manufacturing processes. In October 2010, the FDA again issued a request for more information, including a QT interval study and results from a recently completed trial. Currently, the FDA Action Date for exenatide-LAR is set for January 28, 2012.[1] Exenatide-LAR was approved for use in the European Union in June 2011.[20]

To further complicate the exenatide-LAR landscape, Amylin Pharmaceuticals recently filed a lawsuit against Eli Lilly and Co. alleging that Eli Lilly is breaching their strategic alliance in the marketing of Byetta® and future marketing of Bydureon™ (due to Eli Lilly's plans to simultaneously market linagliptin, a DPP-IV inhibitor).[21] How the resolution of these complex issues will affect patients, providers, and the managed care industry remains to be seen.

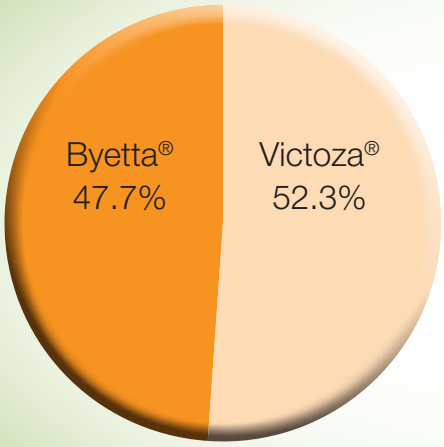
The difference between once- and twice-daily administration may be overshadowed by the potential for once-weekly dosing. It is probable that exenatide-LAR will have the most favorable dosing schedule in the eyes of patients, yet the potential complexity of its administration may discourage some. Difficulty of the reconstitution and administration for each dose of exenatide-LAR may present an initial barrier to increased patient satisfaction and adherence. Currently in Europe, the approved product's packaging includes a patient instruction guide for self-administration, which is more than thirteen pages long.[9]

In terms of efficacy, exenatide-LAR holds an intermediate position within the GLP-1 agonist class. It clearly provides greater glycemic control than its twice-daily counterpart, but it failed to meet noninferiority to liraglutide in the DURATION-6 trial, which was funded by the developers of exenatide-LAR. Accurate cost information for exenatide-LAR is not publicly available at this time since it is still pending approval. Exenatide-LAR will be appealing to payors who value its once-weekly dosing and are unconcerned about its more complicated administration process.

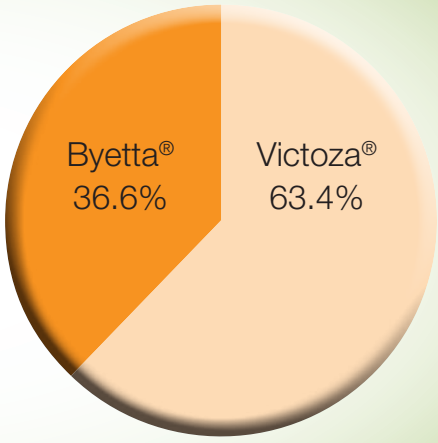
There is no standard regarding how to approach new medication classes within managed care. Approaching the GLP-1 agonist class, which is high in cost compared with some older diabetes medication classes, but supported by national guidelines, is not straightforward. Fortunately, the managed care industry, prescribers, and patients alike now have clinical data available to assist in critically differentiating the members of the GLP-1 agonist class. Excluding cost, liraglutide has demonstrated several advantages over exenatide, including efficacy and dosing schedule. Although these advantages may soon be challenged by the potential approval of exenatide-LAR, the introduction of this once-weekly GLP-1 agonist has been complicated by approval setbacks, a lawsuit amongst its partnering pharmaceutical companies, less than ideal results from the DURATION-6 trial, and its complicated administration. Just as prescribers and patients need to analyze the differences amongst the available GLP-1 agonists, the managed care industry must also carefully evaluate these medications when making decisions that are both strategic and clinically appropriate. As the individual GLP-1 agonists offer unique therapeutic advantages, open formulary access for these agents may prove to be the most clinically appropriate option to improve patient outcomes and overall network satisfaction.

National Market Share Comparisons

TRx NATIONAL MARKET SHARE: GLP-1 AGONISTS[22]



NRx NATIONAL MARKET SHARE: GLP-1 AGONISTS[22]



NOTE: Market share calculated as of August 19, 2011

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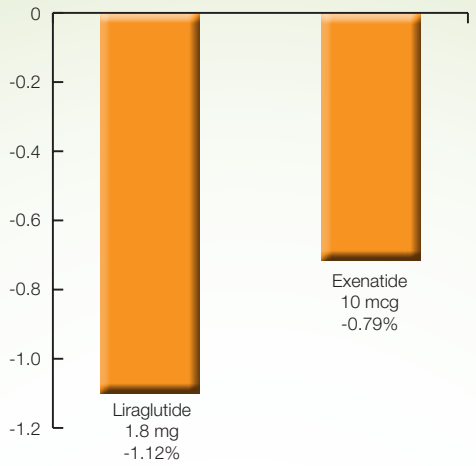
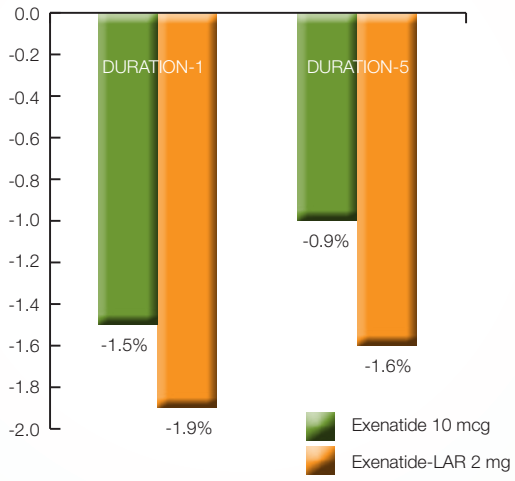
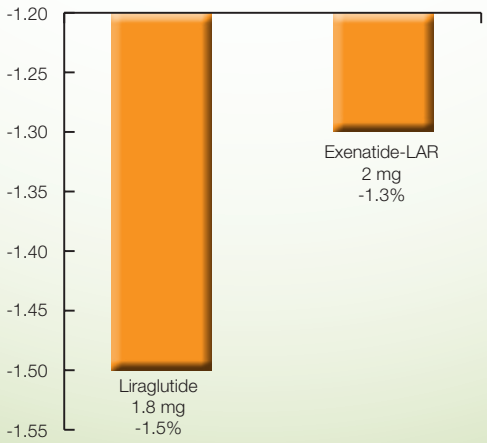
LEAD-6 TRIAL: PERCENT CHANGE IN HbA_{1c} FROM BASELINE[2]



DURATION-1 AND 5 TRIALS: PERCENT CHANGE IN HbA_{1c} FROM BASELINE[5,6]



DURATION-6 TRIAL: PERCENT CHANGE IN HbA_{1c} FROM BASELINE[13]



Addressing Chronic Pain in the Managed Care Setting

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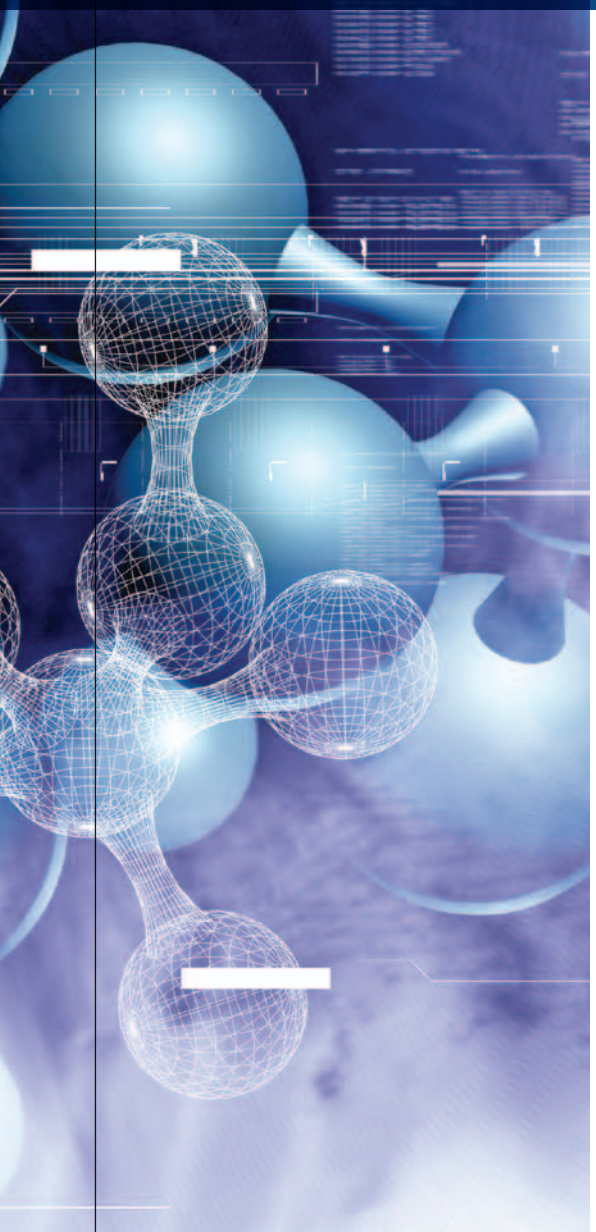

Approximately one-fourth of Americans have chronic or recurrent pain unrelated to a cancer diagnosis. Of these patients, 40 percent proclaim that the pain has a significant effect on their quality of life.[1] There are numerous lifestyle, natural, over-the-counter, and prescription options available to manage acute and chronic pain. These management strategies range from exercise and physical therapy to narcotic analgesics.[2,3] However, while opioids such as fentanyl were once reserved for patients with severe cancer-related pain, this is no longer the case. Today, these agents are just as likely to be prescribed for chronic, and often for acute, conditions unrelated to a cancer diagnosis, such as lower back pain.[4] Indeed, the most commonly prescribed and sold prescription drug in the U.S. in 2010 was the opioid hydrocodone in combination with acetaminophen, followed by simvastatin and lisinopril.[5]

However, unlike antihypertensive and anticholesterol drugs, pain medications carry a high risk of abuse, misuse, and diversion. Between 2002 and 2003, it is estimated that approximately 1 out of 25 opioid prescriptions dispensed in the U.S. were used nonmedically. In 2003, an estimated 13.7 million individuals abused oxycodone, a 13 percent increase over the previous year. The majority of these abusers, according to government statistics, were ages 12 to 34.[6]

It is clear that prescription medications have become the new drugs of choice for recreational use. In the United States, between 1993 and 2005, there was a drastic increase in the nonmedical use of prescription painkillers (343 percent), stimulants (93 percent), tranquilizers (450 percent), and sedatives (225 percent).[7] A major reason that has led to the escalation in nonmedical drug use is increased access to pharmaceuticals. In the past 15 years, there has been a substantial increase in the amount of opioid prescriptions written by prescribers. This has resulted in increased opioid analgesic prescription sales of 347 percent.[8] Additional reasons that may be associated with the increased nonmedical utilization of prescription medications are perceptions of relative safety and purity compared to illicit drugs.

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One explanation for the increased access to pharmaceutical products is the practice of off-label prescribing. A good example of a narcotic frequently prescribed outside U.S. Food and Drug Administration (FDA)-approved labeling is the "lollipop" Actiq® (fentanyl lozenge, Cephalon). Actiq® is currently only approved for use in cancer patients and is recommended to be prescribed only by oncologists.[9] In 2006, however, *The Wall Street Journal* reported that the drug was marketed off-label to other specialties, particularly neurologists. In the first six months of that year, oncologists accounted for just 1 percent of the 187,076 Actiq® prescriptions filled at U.S. retail pharmacies.[10]

The high rate of opioid misuse, coupled with the risk of morbidity and mortality associated with abuse, led the FDA earlier this year to require that manufacturers of all long-acting and extended-release opioid drugs develop a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs outweigh the risks.[11] These include educating clinicians and patients on opportunities to reduce the misuse and misprescribing of opioids; expanding state-based prescription drug monitoring programs; identifying convenient and environmentally responsible ways to remove unused medications from homes; and reducing the number of "pill mills" and the practice of doctor-shopping through law enforcement.

At UPMC Health Plan (UPMCHP), clinical management of opioid agents has prevented many issues of misuse. For instance, UPMCHP requires a prior authorization for all Actiq®, or generic equivalent, prescriptions across all lines of business; through 2010, non-cancer use of this drug is virtually nonexistent across the entire plan. In addition, when UPMCHP removed OxyContin® (oxycodone controlled-release tablet, Purdue Pharma L.P.) from the medication formulary, 13 percent of members who were previously using the drug not only stopped taking it, but did not switch to any other opioid. This suggests that these patients may have been continuing therapy that was not medically necessary or have potentially been participating in pharmaceutical diversion.

Simply ensuring clinically appropriate access to narcotics, however, does not meet UPMCHP's concurrent goals of (1) improving the management and treatment of pain, (2) preventing and addressing issues of addiction, and (3) reducing the risk of diversion and abuse. The fear that patients will abuse opioids is a major reason physicians, particularly primary care physicians, under-treat pain and are reluctant to prescribe chronic opioid therapy. Yet once opioids are prescribed, there is evidence that they do not provide the appropriate follow-up to reduce the risk of abuse.[12,13]

Thus, UPMCHP decided that in addition to managing the problem of pain management and diversion at the pharmacy level, it would address the issue within the physician practices. The health plan first held several focus groups with UPMC health system thought leaders, including primary care physicians, psychiatrists, addiction specialists, pharmacists, and pain-management specialists. These professionals highlighted the need for seamless and integrated care coordination to manage chronic pain patients and reduce the risk of opioid misuse. They also discussed the need for clinicians to better understand pain, its underlying physiology, and its impact on a patient's mental as well as physical health. Finally, they stressed the importance of providing a referral link once a patient's issues exceeded those of the primary clinician's comfort level.

13.7 MILLION

An estimated 13.7 million individuals abused oxycodone in 2003.

The result is a comprehensive pain management program that UPMCHP has implemented which extends to all of the primary care physicians and opioid prescribers within the network. The primary goal of the program is to increase the quality of care for members living with chronic pain. The program objectives include reducing the number of concurrent opioid medications members take and successfully engaging provider-identified members in care management services for opioid abuse or addiction. Additional objectives include improving the overall management of opioid costs and achieving positive provider participation and satisfaction with the program and care management/pharmacist services.

In the design of the UPMCHP pain management program, patient identification is the first critical component. Physicians are aware that improper opioid management and misuse is a problem; however, many of these providers lack adequate information to identify which patients within their practice are at risk. Furthermore, many patients receive opioid prescriptions from multiple prescribers without the knowledge of the PCP, creating challenges of care coordination and patient safety. To assist network providers in overcoming this therapeutic barrier, UPMCHP has developed a proprietary algorithm to identify chronic-pain patients that may be at an increased risk of diversion activity or present potential concerns of therapeutic duplication or opioid abuse. For each primary care physician, a patient-specific target list is developed that includes each patient's pharmaceutical claims information. These alerts are then disseminated to the appropriate PCPs for therapeutic review. All other prescribers of opioids who are not the patient's PCP are also copied on this communication. In addition, UPMCHP has developed and distributes a pain management toolkit designed to assist its network providers in making appropriate therapeutic decisions for these patient opportunities.

The Toolkit

The toolkit contains several components:

- A letter to the physician explaining the program
- Patient assessment guidelines
- A summary of pain etiology and treatment options
- Acute pain strategies and resources for management and follow-up
- Chronic pain strategies and resources for management and follow-up
- Multidisciplinary team support and referral options
- Tools for proper documentation and pain management

The kit provides clear guidelines for the use of opioids in chronic pain, noting that they are "not recommended as the initial or primary treatment strategy" and that non-pharmacologic therapies targeting pain and function should be considered first. Clinicians are encouraged to include strategies for managing the physical, emotional, social, and vocational needs of the patient. This often requires a multidisciplinary team including a physical therapist, pain specialist, and/or psychologist. When prescribing opioids, it also highlights the four "A's" for ongoing monitoring of chronic pain patients: analgesia, activities of daily living, adverse drug events, and aberrant drug-related behaviors.[14]

The pain management kit identifies acute pain management tools such as dose titration, adjuvant therapy, the use of alternative formulations and routes of administration, and options to modify or change opioid therapy. It also provides an equianalgesic chart for opioid dose conversions. Part of the kit's education for acute pain is to urge physicians to plan for opioid discontinuation even upon initiation. This includes educating patients on using the drug as prescribed and discontinuing as soon as possible. When the length of acute therapy extends beyond two weeks, physicians are instructed how to taper the dose over several days to avoid adverse events.

The kit also highlights patient risks for opioid abuse, which includes a personal or family history of alcohol and/or drug abuse, younger age, and comorbid psychiatric conditions. Additionally, this resource urges clinicians to monitor patients based on their risk level.[15-19]

Finally, the kit also provides clues as to when providers should suspect misuse problems and how to manage these issues when they arise. For instance, if a patient presents with aberrant drug-related behavior, such as requesting prolonged therapy for acute pain despite a reasonable dose adjustment, a referral to a pain specialist/treatment team may be appropriate. Due to the high abuse potential and addictive properties of opioids, chronic pain patients often develop physical and psychological dependencies to these pharmaceuticals. At the first signs of dependency, primary care physicians are encouraged to perform a brief intervention and, when appropriate, refer these patients to qualified specialists who can responsibly manage dependent patients. Whether these

OPIOID DEPENDENCE: PHARMACEUTICAL TREATMENT OPTIONS	
Suboxone® (buprenorphine/ naloxone) Sublingual Film	• Available as 2 mg/0.5 mg or 8 mg/2 mg buprenorphine/naloxone once-daily sublingual film[21] • Buprenorphine demonstrates a ceiling effect where the respiratory depression effect plateaus, and patients are less likely to overdose on the drug[22] • If injected, naloxone attenuates the effects of buprenorphine and precipitates withdrawal in individuals dependent on full opioid agonists but has no significant effect when taken sublingually[21] • Intended for unsupervised use
Subutex® (buprenorphine)	• Single entity buprenorphine product, available in 2 mg and 8 mg sublingual tablets[23] • Generically available • Does not contain naloxone as a method to reduce abuse potential; intended for supervised use
Vivitrol® (naltrexone)	• Indicated for prevention of relapse to opioid dependence (following opioid detoxification)[24] • Requires physician office administration of 280 mg intramuscular injection every four weeks[24] • Higher monthly cost than other available opioid dependence treatment options
Methadone	• First treatment modality for opioid dependence • Available in 5 mg and 10 mg scored tablets; also comes in disket and liquid formulations for clinic use only • Typical initial dose is 20 to 30 mg once daily; typical maintenance dose is 80 to 120 mg per day[22] • For the management of opioid dependence, methadone must be administered in a methadone treatment center • Low cost for medication, higher cost for daily methadone clinic charges

patients have developed dependencies through appropriate medical use or from recreational abuse, specialized management programs, such as Suboxone® clinics, have demonstrated significant clinical and financial advantages when compared to primary care management.[20] Appropriate options for patient referrals are an essential component of the UPMCHP pain management program.

One Year Later

A year after the pain management program was implemented, the reaction has been overwhelmingly positive. The letters and toolkits have been distributed to 1,182 primary care physicians, about a third of whom have sent in referral request forms. Another 1,076 prescribers also received copies of the letters, which include the prescription claim history of the identified patient. Of the 670 PCP referral requests received by late February 2011, nearly 19 percent (126) requested that care management or a pharmacist contact the office. The services provided fell into one of four areas:

- Care coordination support through the plan's comprehensive care management program, behavioral health referrals, or other programs to discuss and review the providers' pain management plan. To date, 35 percent of care management requests have been for care coordination.
- Pain specialist referrals to help patients better manage their pain. To date, 32 percent of requests for care management have been for pain specialist referrals.
- Member outreach services, which provide member support such as transportation to appointments, assistance with various psychosocial issues, and education to reinforce the importance of the treatment plan. To date, 23 percent of care management requests have been for member outreach services.
- Management of abuse issues. To date, 10 percent of care management requests have been for managing potential abuse issues. For example, physicians requesting to discuss with a UPMCHP pharmacist a member's drug profile in instances where members were getting opiates from multiple prescribers.

Beyond the Toolkit

In addition to the management program and sending quarterly letters and toolkit folders to practices, UPMCHP also held an accredited continuing education program on pain management. UPMCHP hopes to provide similar programs in the future. It also plans to incorporate physician detailing into the program by meeting with physicians identified as high prescribers of opioid drugs and providing personalized education on the pain management program and toolkit as well as the plan's pharmacist and care management resources.

All components of the program—from sending the doctor the letters and toolkit, to receiving requests for referrals, to providing physician counseling—are documented.

The key lesson from this program is that simply managing opioid use at the formulary and utilization management levels is not enough. The chronic pain that millions of members experience is real, and opioids are an important tool in a physician's arsenal for addressing that pain. Educating clinicians about the appropriate use of opioids, providing targeted and actionable member information and tools to assist them in identifying the warning signs of misuse, and providing strong health plan resources and support once they encounter problems with either the patient or in managing the patient's pain is crucial. These components provide the type of comprehensive approach necessary to meet the simultaneous goals of reducing pain while avoiding misuse.

Editorial assistance for this article was provided by Debra Gordon, MS.

UPMC Guidelines for Initial Pain Assessment

- Detailed history of pain, including use of pain assessment scales
- Full family history, social history, and psychosocial assessments
- Past medical records and diagnostic studies
- Physical and neurological exam
- Diagnostic workup to determine cause of pain

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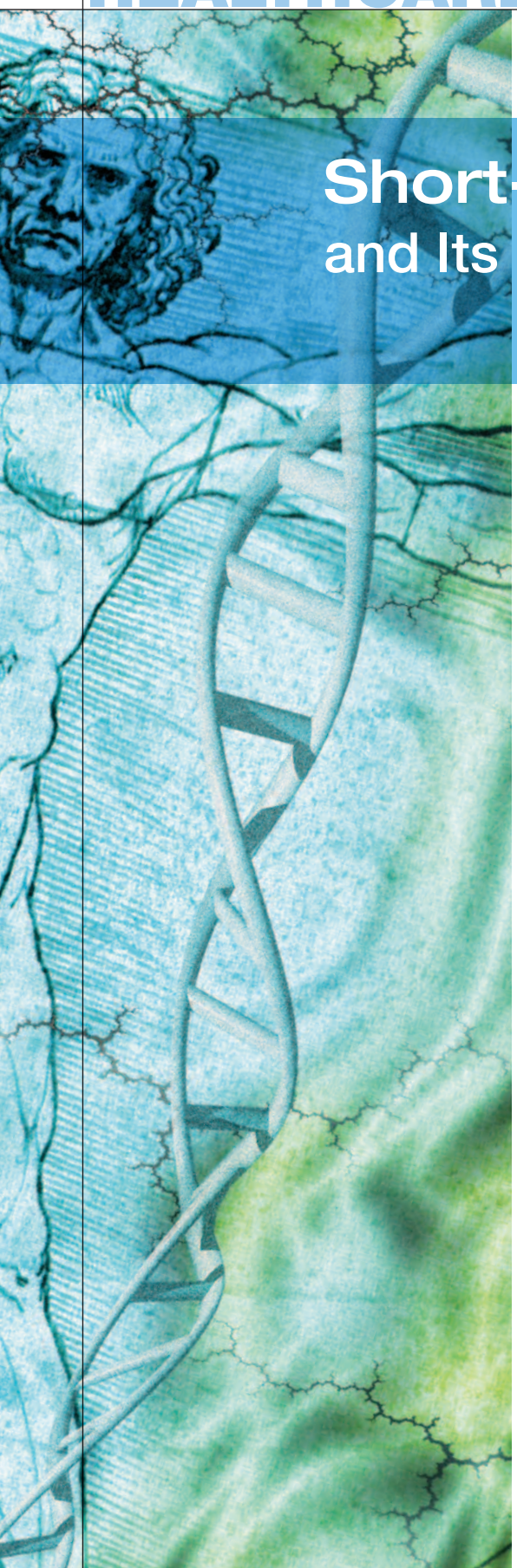

Short-Cycle Dispensing and Its Role in Healthcare Reform

Norrie Thomas, PhD, MS, RPh, President, Manchester Square Group, Senior Fellow, Center for Leading Healthcare Change, University of Minnesota College of Pharmacy

One provision of the Patient Protection and Affordable Care Act stipulates that Medicare Part D plans employ utilization management techniques to reduce the per-fill amount of prescription medications dispensed to Medicare beneficiaries in long-term care facilities. The aim behind the provision, known as short-cycle dispensing, is to cut down on unused medications through reducing the per-fill quantity from the traditional 30-day fill to biweekly, weekly, or daily fills.

When the regulation was first proposed, the belief was that shorter fills would result in less medication waste—the unused medication resulting from facility discharges, medication changes, death, or other causes.

As industry professionals began to closely study the idea of medication waste and provide focused feedback, it became clear that harnessing cost savings without unduly burdening facilities, pharmacies, or those in charge of tracking the regulation's financial impact was a challenge. There is also a paucity of baseline data, hampering the ability to measure progress as short-cycle dispensing is broadly implemented.

What was supposed to become effective in January 2011 has been pushed back to January 1, 2013. This extension is intended to give long-term care facilities time to adjust to the requirement and to allow for the implementation of monitoring techniques that will pinpoint cost savings and waste reduction. Exactly how the regulation will affect payor reimbursement hinges on many factors.

Medicare Cost Savings Was Impetus

The new regulation emerged in November 2010 when the Centers for Medicare & Medicaid Services (CMS) issued a Notice of Proposed Rule Making. This recommendation advised that the dispensing of all brand-name drugs to Part D beneficiaries in long-term care facilities be in increments of seven days or less.[1] Through public feedback, including requests for more research from the lawmakers themselves, the regulation now requires the dispensing of all brand-name drugs in 14-day-or-less increments. This will affect Part D patients residing in long-term care facilities and applies only to orally administered solid dosage forms. The rule, as it stands, also requires Part D plans to gather and report data

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both on dispensing methodology and the amount of unused medications for each dispensing event.[2]

The initial assessment of short-cycle dispensing estimated an overall Medicare cost savings of $5.7 billion from 2012 to 2019.[3] This seemed to ensure the provision would move forward. However, concern arose over the initial proposal to shorten all brand-name fills to seven days or less. It was believed there was a lack of data indicating such a change would indeed reduce medication waste. Additionally, many industry leaders believed the focus was on the wrong patient population. In long-term care facilities, the average length of stay is 2.5 years.[3]

This population—those receiving prescription drug coverage through the Medicare Part D program—is likely to be on multiple medications but unlikely to require the type of changes that would benefit from adhering to a short-cycle dispensing regimen. These patients take an average of 8 to 10 maintenance medications per day and do not require frequent modifications to their drug regimens. However, Medicare Part A beneficiaries entering a long-term skilled nursing or rehabilitation facility average a 20-to 30-day stay.[4] These patients have a much higher turnover rate as Medicare will cover only the first 100 days of their stay. This population might be a more appropriate target to achieve the cost-saving benefits of short-cycle dispensing due to the shorter stay and high possibility of therapy modifications.

Cost Savings Challenged

An industry study of unused medication within long-term care facilities illustrated why such a change would not likely yield the anticipated cost savings.[5] The study was commissioned by the Long Term Care Pharmacy Alliance and released in January 2011 as the short-cycle dispensing regulation appeared to be moving ahead with the seven-day fill requirement. The study, based on eight long-term care pharmacies, examined data on both dispensed and returned prescriptions from long-term care nursing facilities.

The study determined that all returned oral solid prescriptions containing unused medications equaled 6.1 percent of all dispensed prescriptions in these long-term care facilities. The study also determined that the cost to Medicare Part D plans for all returned oral solid prescriptions was 2.9 percent of all dispensed prescriptions. On average, returned prescriptions contain about half of the dispensed doses. The total yearly cost of unused oral solid medication in these long-term care facilities was found to be $125 million. Yet applying a seven-day fill requirement to approximately 59 million brand and generic oral solid prescriptions annually would translate into an additional 194 million prescriptions dispensed. With an average dispensing fee of $4.74 for each of those additional prescriptions, the net cost comes to more than $820 million charged to Part D plans.[6]

A second analysis included in the study evaluated a sample of 10.3 million Medicare Part D dispensed prescriptions. Researchers assessed proportions of brand versus generic products, oral solid versus other dosage forms, and a breakout by prescription ingredient cost. The analysis concluded that requiring a seven-day fill for all oral solid brand-name products would result in 46 million additional prescriptions dispensed and more than $150 million in incremental costs to Part D plans each year.[6]

The researchers concluded that limiting the seven-day fills to only high-cost brand products with ingredient costs of more than $400 per prescription "may result in modest savings" of about $10 million annually to Part D plans. If the seven-day requirement applied to generic products, the stipulation would result in 154 million additional dispensings and $700 million in additional costs to Part D plans annually.[6] The study found no significant savings opportunities for generic products at any level of medication cost.

"While it may appear that implementing a short-cycle dispensing regimen will necessarily generate savings in the

$125 MILLION

The total yearly cost of unused oral solid medication in certain long-term care facilities

Medicare Part D program, the analysis shows that any savings achieved by reducing unused medications are overwhelmingly exceeded by the additional dispensing fees," as stated by the researchers.

In a March 14, 2011 letter to CMS Administrator Donald Berwick, groups such as the Long Term Care Pharmacy Alliance, the Academy of Managed Care Pharmacy, the American Pharmacist Association, American Health Care Association, and National Alliance of State Pharmacy Associations raised concerns about the proposed rule and pointed out that industry "shares CMS's interest in reducing waste in the provision of pharmaceuticals."[8] The letter requested an additional study to assess the regulation's "true systemic costs and potential impacts on patient care before implementation." Those industry groups proposed a pilot program to study how to implement a short-cycle dispensing regulation that would garner cost savings and waste reduction.

CMS is encouraging short-cycle dispensing to be voluntarily applied to generics and has proposed that long-term care facilities steer that application. The rule suggests Part D sponsors facilitate the voluntary inclusion of generics in 14-day-or-less dispensing.

Currently, no plan for a pilot project exists, and industry insiders expect the proposed rule to move forward with the January 1, 2013 implementation date. Two weeks after the industry letter was sent, Sens. Ron Wyden (D-Ore.), Debbie Stabenow (D-Mich.), and Benjamin L. Cardin (D-Md.), also wrote to Berwick. They said the seven-day-or-less short-cycle dispensing rule lacked sufficient data "to gauge the underlying savings associated with this provision." Others urged CMS to seek input from stakeholders around the issue of enforcement in consideration that facilities could be in violation of the rule without intent.[8]

Impact and Highlights

Here are some interesting points about the final rule on short-cycle dispensing:

- CMS is encouraging short-cycle dispensing to be voluntarily applied to generics and has proposed that long-term care facilities steer that application. The rule itself suggests Part D sponsors facilitate the voluntary inclusion of generics in 14-day-or-less dispensing.[2]
- All unused drugs must be reported by the Part D plan sponsor; however, CMS did eliminate a proposed requirement for all unused medications to be physically returned to the pharmacy.[2]
- The reporting requirement will be waived by CMS for those pharmacies that agree to use seven-day-or-less dispensing for both brand and generic medications.[2]
- Exempt medications include liquids, antibiotics, and drugs in original packaging.[2]
- Long-term care facilities are allowed to select the dispensing methodology used as long as the methodology is "uniform" within the facility. The provision applies to all Part D sponsors and pharmacies dispensing to beneficiaries within the facility. "Uniform dispensing techniques" include the dispensing increment, such as 7-day or 14-day, as well as the dispensing methodology and the packaging system.[2]
- Part D sponsors should not request credits for dispensed medications that are not consumed by the patient.[2]

While the new regulations produce considerable administrative challenges, the final rule as it stands appears to be an improvement over the initial proposal. Further data regarding short-cycle dispensing will be necessary to elucidate functional procedures to address the issue of medication waste without placing an excessive burden upon facilities, pharmacies, or payors. Whether it's governmental cost savings, an increase in costs to Part D plans, or a budget-neutral procedural shift, the end result remains to be seen. In the ensuing years, the effect of short-cycle dispensing policies on pharmaceutical dispensing, tracking, disposal, and selection will be interesting to witness.

The Cost of Wasted Pharmaceuticals

As stated by the joint pharmacy associations, we all share CMS's interest in reducing waste in the provision of pharmaceuticals. Therefore, finding ways to reduce waste is an important goal and one worth our attention. One thing the researchers did not focus on is the cost of wasted pharmaceuticals; the cost of waste includes the burden of wasted pharmaceuticals on the environment and the burden on the workforce to spend time and energy destroying wasted product. If short-cycle dispensing is not the answer, what are other approaches that we should consider? Introducing new policy often leads to unintended consequences and unanticipated changes. What are the changes that might occur in the practice of pharmacy based on reducing the amount of wasted pharmaceuticals? Some potential changes might be:

If short-cycle dispensing is not the answer, what are other approaches that we should consider?

- Unit-dose packaging, including ability to reuse unopened packages
- Environmental grading system for all medications, including cost of managing waste
- Medication Therapy Management (MTM) required for quantities over 30 days
- The end of the 90-day supply
- New technology to allow for automated dispensing of unit dose
- Medication tracking systems linked to unit-of-use packaging
- Commercial pharmacy benefit programs may consider integrating medication adherence programs with medication surveillance for prescriptions dispensed with quantities over 30 days

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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.

References: 1. Blonde L, Meriläinen M, Karwe V, Raskin P, for the TITRATE™ Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets—the TITRATE™ study. *Diabetes Obes Metab.* 2009;11(6):623-631. **2.** American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care.* 2010;33(suppl 1):S11-S61.

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 $AUC_{(0\text{-}2h)}$ 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

Manufactured for: Novo Nordisk Inc., Princeton, NJ 08540, www.novonordisk-us.com
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark
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Levemir®
insulin detemir (rDNA origin) injection

Focus on Appropriate Antipsychotic Utilization

Robert L. Dufresne, PhD, PhD, BCPS, BCPP, Psychiatric Pharmacotherapy Specialist, Providence VA Medical Center, Professor of Pharmacy, University of Rhode Island College of Pharmacy

The atypical antipsychotic class (also known as second-generation antipsychotics) accounts for significant drug spend in both commercial and government health plans. This class presents many challenges to utilization management and many organizations are searching for strategic and clinically appropriate solutions. Although dramatic changes are on the horizon as many of these branded drugs go generic in the next four years, health plans are still faced with today's issue of managing antipsychotic utilization for patients with schizophrenia and related psychotic disorders. The goal is to utilize the available finances and pharmacologic agents more efficiently to optimize treatment options and provide the best possible care for this patient population.

The Changing Landscape

The World Health Organization (WHO) attributes 14 percent of the global burden of disease to psychiatric disorders, primarily schizophrenia, depression, substance abuse, and related psychotic disorders.[1] Furthermore, neuropsychiatric disorders account globally for one-third of the years of healthy life lost due to disability for individuals ages 15 years or older.[1] In light of this growing disease burden, governments, healthcare payors, and the medical community have become more aware of the need to pay greater attention to promoting mental health. Early detection and appropriate treatment not only offer significant public health benefits, but also can bring economic benefits.[1]

Drug coverage for schizophrenia and related psychotic disorders is primarily funded by the government, with Medicaid picking up 44 percent of treatment costs for schizophrenic patients and Medicare Part D accounting for another 24 percent. Commercial insurers fund roughly 23 percent of the bill, with 9 percent coming from other sources.[2]

When it comes to treating mental illness, global sales of psychiatric drugs grew from $41.2 billion in 2005 to $50 billion in 2009, an increase of 21.4 percent in four years. Most of this growth came from increased sales of atypical antipsychotics. In 2010, antipsychotic medication prescriptions in the U.S. accounted for approximately $15 billion.[2]

The typical antipsychotics (also known as first-generation antipsychotics) have been on the market for decades and are all off-patent and subject to generic competition. However, despite the low prices of typical antipsychotics, psychiatric specialists often favor the use of atypical antipsychotics due to a purported greater efficacy in

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treating the negative symptoms of schizophrenia with a lower risk for extrapyramidal symptoms, such as drug-induced parkinsonism, akathisia, and dystonias.[2] More importantly, the use of atypical antipsychotics rather than typical antipsychotics results in a much lower incidence of Tardive Dyskinesia, which is a syndrome consisting of potentially persistent choreoathetoid movements that can occur due to prolonged treatment with these agents.[3] Of the atypical antipsychotics, clozapine and risperidone are currently subject to generic competition, and most of the other atypical agents will lose their patent protection by 2015 (see Table 1).[2]

Even with this changing landscape, it's important to note that antipsychotic prescriptions are only a part of the total cost of care for schizophrenia. Twenty-five percent of the U.S. mental health expenditures are for inpatient mental health treatment. Hospitalization is more costly than outpatient services provided by psychiatrists, psychologists, and social workers combined. Psychiatric hospitalization has a threefold higher price tag than outpatient antipsychotic medications.[4]

The goal of therapy is to identify schizophrenic patients early in their disease, treat them appropriately with antipsychotic medication to prevent relapse, and enable them to improve their quality of life and productivity. Given the significant individual variability in response, mental health advocates and experts support the availability of a variety of antipsychotic medications for patients with schizophrenia so that the right medication can be found to prevent costly and devastating relapses.[5-7]

Table 1 ORAL ATYPICAL ANTIPSYCHOTICS

Drug	Brand Name	Manufacturer	Patent Expiration*
Aripiprazole	Abilify®	BMS/Otsuka	4/2015
Asenapine	Saphris®	Merck	6/2015
Clozapine	Clozaril®	Novartis/generics	12/2005
Iloperidone	Fanapt®	Novartis/Vanda	11/2011
Lurasidone	Latuda®	Sunovion	7/2013
Olanzapine	Zyprexa®	Lilly	10/2011
Paliperidone	Invega®	Janssen	4/2012
Quetiapine	Seroquel®	AstraZeneca	3/2012
Risperidone	Risperdal®	Janssen/generics	6/2010
Ziprasidone	Geodon®	Pfizer	3/2012

*Earliest date that a generic could be available; however, other circumstances could extend or shorten the exclusivity period.

Problem Areas in Antipsychotic Utilization

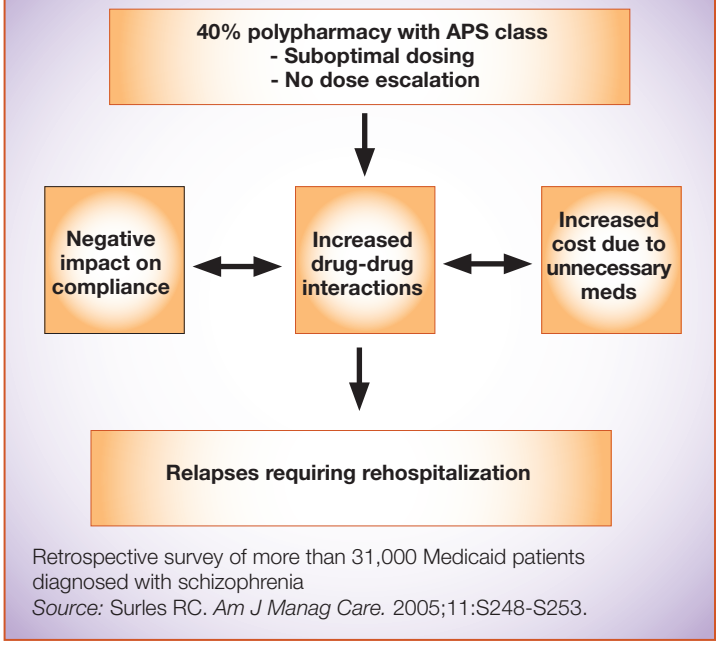
Inappropriate Utilization

The goal of treatment is to get the right medication to the right patient at the right time to manage a patient's schizophrenia. However, there are times when utilization patterns seen with antipsychotics have no evidence-based data to support them. One of these examples is antipsychotic polypharmacy, which is the concurrent treatment with more than one antipsychotic medication. Combination treatment with more than one antipsychotic agent has been reported to occur in up to 40 percent of patients on antipsychotics.[8,9] Currently, there are no evidence-based guidelines to support this practice. Potential concerns regarding antipsychotic combinations include the possibility of higher than necessary total dosages, an increased side effect profile, drug-drug interactions, increased rates of noncompliance, difficulties in determining cause and effect of multiple treatments, higher cost, and poorly documented risks and benefits of combination therapy (see Fig. 2, page 28).[9] Educational group interventions and monthly audit feedback were shown to be successful in reducing antipsychotic polytherapy in one psychiatric facility.[10]

Appropriately transitioning from one atypical to another is also a challenge. There are times when a patient is being switched from one therapy to another where there is an overlap in treatment as the patient is titrated off one agent and titrated up on another agent. These situations require careful monitoring on behalf of the providers to ensure proper management of the patient's disease and limit relapse. Dosing that is either suboptimal or that exceeds the approved FDA labeling for an antipsychotic is another problem area.

An additional concern involves off-label use of antipsychotics, as highlighted in a report from the Office of Inspector General (OIG) released May 4, 2011. The OIG found that 88 percent of Medicare claims for atypical antipsychotics prescribed to patients in nursing homes were for dementia. FDA-approved labeling for the atypical antipsychotic class contains a black-box warning stating that elderly patients with dementia-related psychoses treated with such drugs are at an increased risk of death.[11]

Fig. 2 **DANGERS OF POLYPHARMACY WITH ATYPICAL ANTIPSYCHOTICS**



Retrospective survey of more than 31,000 Medicaid patients diagnosed with schizophrenia
Source: Surles RC. *Am J Manag Care.* 2005;11:S248-S253.

Impact of Increasing Controls and Restrictions on Antipsychotics

Managing the antipsychotic class for a vulnerable patient population can be a difficult challenge for any health plan and requires a fine balance. Implementing too many restrictions may have unintended consequences when patients discontinue their treatment, resulting in increased ER visits and hospital admissions. Currently, there are examples in the literature of formulary management programs that have resulted in treatment nonadherence and even discontinuation, resulting in relapse, without demonstrating cost savings to the health plan.[12-16] Creative utilization management techniques should be investigated to efficiently and effectively reduce cost and promote medication continuity while improving outcomes.[17]

Adherence

Medication adherence problems are well-documented in schizophrenic patients. Some of the reasons for non-adherence include:[18,19]

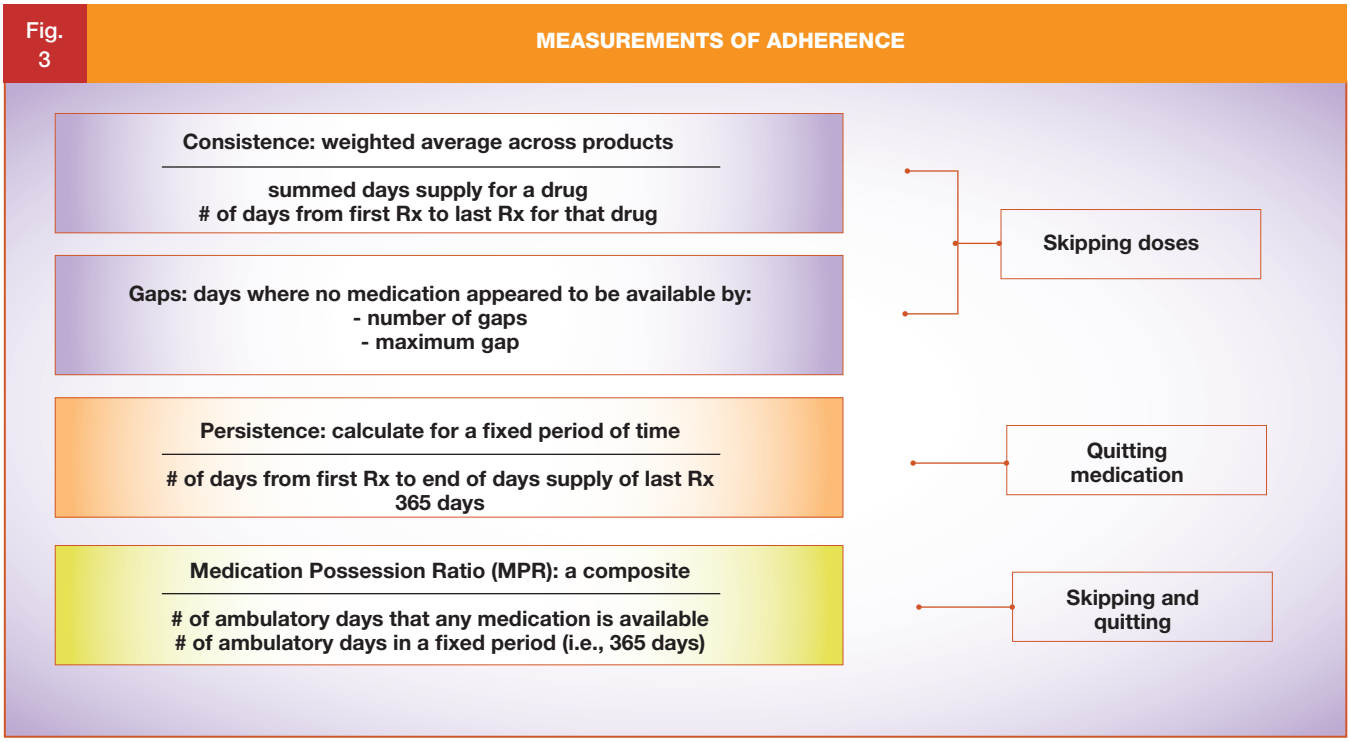
- Lack of a structured schedule that may increase the difficulty in adherence to medication, especially in a patient with disorganized thinking
- Many patients lack education or awareness of their illness and may not see a need to take their medication
- Patients who are feeling better may think they no longer need medication and discontinue it without consulting with their provider(s)
- Side effects of antipsychotics may discourage some patients from taking their medication and often cease immediately after stopping treatment; however, relapse is insidious and may take some time to occur
- Substance abuse and other comorbidities may negatively impact a patient's ability to conduct daily activities and to adhere to medication
- Patients with worsening symptoms may be incapable of adherence without assistance

Non-adherence may make patients susceptible to relapses, which may slow recovery and potentially result in more frequent hospitalizations. After each relapse, regaining the previous level of functioning may be harder and less likely. Schizophrenia can become more resistant to treatment after multiple relapses, which only emphasizes the importance of compliance.[19-21]

There are a number of analytical tools and calculations available to assess compliance in this population. Two tools, "Consistence" and "Gaps," both evaluate whether patients are skipping medications. "Consistence" looks at a weighted average of treatment episodes, and "Gaps" is a simpler method of looking at days without medication. Persistence evaluates whether patients stop their medication, and assumes a continuous prescription over a set time period (see Fig. 3, page 29).[22]

Medication Possession Ratio (MPR) is the most commonly used calculation to assess compliance since it evaluates both skipping and stopping medication. It is a composite of the number of days that any medication is available in a fixed period (i.e., 365 days). Patients who have a poor MPR or a history of non-adherence on oral antipsychotics may be good candidates for long-acting injectable antipsychotics. This is an additional tool in the armamentarium to maintain schizophrenic patients' therapy and prevent relapses.[22]

As mentioned earlier, many of the predictors of non-adherence are commonly seen in schizophrenic patients. They often have comorbidities such as depression and substance abuse; they lack insight into their illness and the importance of staying on their medication; side effects of the antipsychotics may be



a deterrent to taking them; and complexity of the treatment regimen and costs can also be barriers to compliance.[18]

A survey of U.S. physicians estimated that an average of 25 percent or more of their psychiatric patients skipped or reduced doses of medication. More disturbingly, an average of 23 percent of schizophrenic patients were estimated to discontinue therapy altogether. Survey respondents believed that an average of 19 percent of patients did not fill prescriptions for their psychiatric medications.[2]

Providers can help improve patient adherence by implementing various strategies. First and foremost, noncompliant patients need to be identified and this information must be communicated with physicians. Physicians can simplify a regimen where possible (e.g., QD dosing vs. TID or once-monthly injections) and try medications with improved side effect profiles if that is the underlying reason for medication discontinuation. Clear, simple instructions can be given to the patient, as well as family members and friends to support the patient.[2]

Surles[8] noted that treatment compliance is crucial in terms of clinical outcomes, as well as cost containment. Poor compliance is associated with a higher risk of relapse requiring costly hospitalization. And as former Surgeon General C. Everett Koop would say, "Drugs don't work in patients who don't take them."[23]

Antipsychotic Prescription Analyzer

The Antipsychotic Prescription Analyzer (APA tool) is an interactive software tool that has been used by more than 100 health plans to analyze their antipsychotic utilization. This unbranded tool was developed by the Health Economics and Outcomes Research team at Janssen. The APA tool analyzes pharmacy claim data by calculating utilization measures related to important quality-of-care issues such as dosing, switching, concomitant use, medication possession ratio, maximum gaps in therapy, and cost. The tool also offers the option to create reports based on individual prescriber utilization, allowing for targeted education.

In addition to commercial health plans, the APA tool has been used by state Medicaid plans, managed Medicaid plans, Medicare Part D plans, Department of Corrections, and the Veterans Integrated Service Networks (VISNs).

Here are three examples of quality initiatives that were done by a commercial plan, a state Medicaid plan, and a Medicare Part D plan in order to obtain cost reductions and ensure appropriate prescribing:

A large commercial plan in the Northeast ran their pharmacy claims data through the Antipsychotic Prescription Analyzer to identify quality-improvement opportunities. They found a significant percentage of low-dose quetiap-

ine that had been prescribed by physicians in their health plan for insomnia at a dose of 25 mg qHS. Clinical studies indicate that the antipsychotic effect of quetiapine usually occurs in the range of 400–800 mg/day. There is a lack of supporting evidence for the use of quetiapine in the treatment of insomnia, and there were less costly and clinically proven sedative hypnotics on the formulary for insomnia. The health plan sent educational letters to the doctors who were prescribing quetiapine as a hypnotic with a list of their patients who were candidates to switch to less costly generic sedative hypnotics on their formulary. This educational campaign resulted in significant cost savings for the health plan while minimizing side effects to these patients.[24]

A Medicaid plan in the South wanted to identify opportunities for quality improvement and cost reduction with an analysis of antipsychotic prescribing trends within a fee-for-service Medicaid organization. The plan found that high-cost, low-evidence prescribing patterns (e.g., antipsychotic polypharmacy, high dose, high frequency) were based on weak or little systematic clinical evidence. It was also noted that long-acting injectables had the highest MPR at 0.87, followed by oral atypical antipsychotics at 0.83 and then oral typical antipsychotics at 0.79. The plan initiated an educational activity with targeted communication aimed at doctors prescribing high-dose therapy and antipsychotic polypharmacy. This dose optimization program directed toward physicians created significant cost savings for the plan. In addition, physicians were alerted of patients who were identified as being nonadherent. Patients with significant gaps in their oral therapy were candidates for long-acting injectables, and the plan estimated significant cost avoidance in transitioning these non-compliant patients onto long-acting injectables to prevent costly relapses.[25]

A large national Medicare Part D plan also ran the Antipsychotic Prescription Analyzer to look at opportunities for quality improvement and cost reduction in non-institutionalized elderly (EB >65 years old) and non-elderly (NEB<65 years old) beneficiaries on antipsychotics. They evaluated 571,956 antipsychotic claims for 91,027 patients. Non-elderly patients accounted for the larger number of antipsychotics compared to elderly patients. Antipsychotic dosing exceeded FDA-approved labeling more frequently among non-elderly vs. elderly patients, and polypharmacy was also more prevalent in the non-elderly patients. Medication possession ratios did not differ significantly between the two groups and was above 80 percent for both. Educational initiatives were rolled out to providers who prescribed high-dose therapy and concomitant antipsychotics based on weak or little systematic clinical evidence. Inappropriate prescribing was found to be the greatest contributor to increased atypical antipsychotic costs. By instituting a dose optimization program, the plan was able to realize significant cost savings in its antipsychotic drug spend.[26]

400-800 MG/DAY

As indicated by clinical studies, the antipsychotic effect of quetiapine usually occurs in this range. Low-dose therapy for insomnia lacks sufficient clinical evidence.

These examples highlight some of the features of the Antipsychotic Prescription Analyzer in providing data necessary to identify quality-improvement opportunities in the area of antipsychotic utilization and to reduce costs to the health plan.

Quality Measures

Mental health has been identified as a priority condition for outcomes measurement and Episode of Care Models by the Department of Health & Human Services (DHHS) and the National Quality Forum (NQF).[27] The National Council on Quality Assurance (NCQA) already has several measurements in the mental health area that have been built into HEDIS (Health Effectiveness Data Information Set). These include: Follow-up after hospitalization for mental illness at seven days and 30 days to prevent relapses. Measures are also being developed to address the cost of care with high hospital readmission rates, poor care coordination, polypharmacy, and low medication adherence.[28]

The APA tool can help identify some of these quality measures within a population, along with an additional tool, entitled, "Assessment for Quality Improvement and Risk Evaluation" (QI/RE). The QI/RE tool is available to

health plans to assist in identifying opportunities to improve treatment for patients with schizophrenia. This tool uses both medical and pharmacy claim data to profile adherence rates, hospitalizations, and predictors of future non-adherence and hospitalization.[19] More information about these tools is available from your local Janssen account executive or Janssen Health Outcomes Liaison.

Conclusions

Managing the appropriate utilization of antipsychotic therapy for patients with schizophrenia is a large undertaking for a health plan. The antipsychotic class of drugs presents many challenges with appropriate selection, dosing, side effects, cost, and compliance issues. Creative and effective formulary management tools must be developed to promote appropriate utilization and inspire medication adherence within this patient population.

Nonadherence to pharmaceutical therapy is common when patients are required to take medications on a chronic basis, and it is especially problematic in vulnerable schizophrenic patients. There are many barriers to patient adherence in the mental health arena, including forgetting to take the medication, feeling that the medication is unnecessary due to lack of insight into their illness, or disliking the side effects of the medication.

Patients with schizophrenia who are non-compliant are more likely to experience relapse of symptoms and repeated hospitalizations. With each relapse, the likelihood that a patient returns to his or her baseline level of functioning declines.

There are tools available to help plans analyze antipsychotic utilization and to help them with quality measures that are being adopted in the mental health arena. These tools can identify non-compliant patients and inappropriate prescribing, so that targeted interventions can be done to educate providers and improve patient outcomes while decreasing overall costs.

Editorial assistance for this article was provided by Arlene Price, PharmD.

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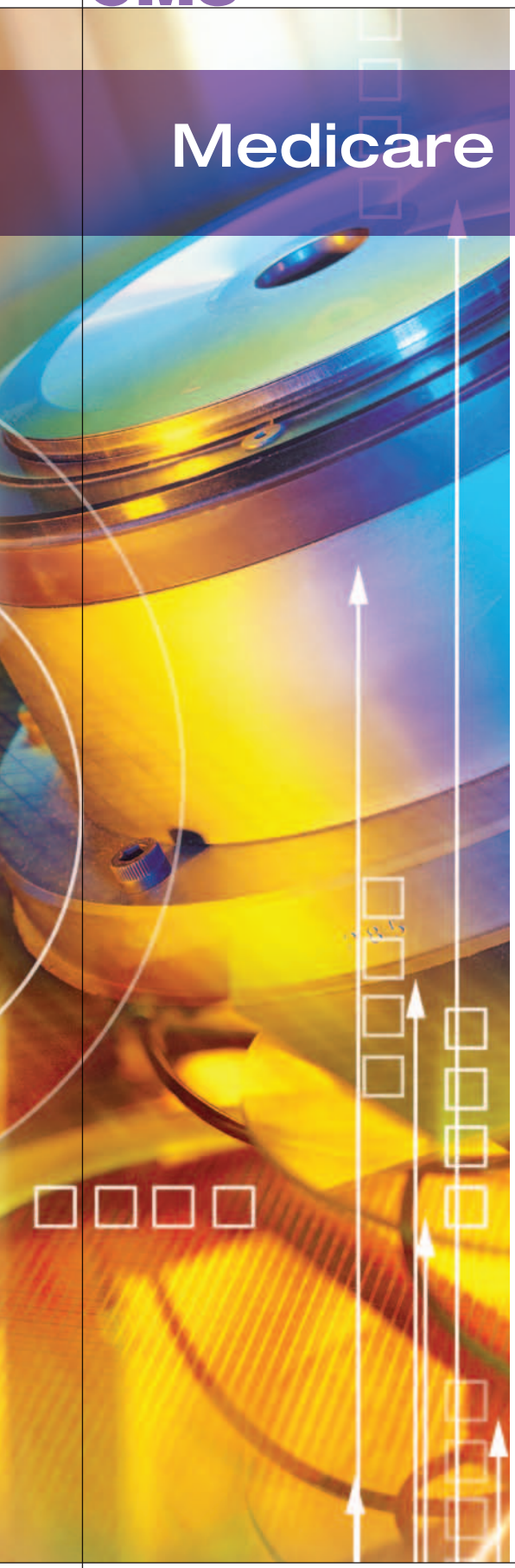

Medicare Stars: Getting to Five

Mesfin Tegenu, MS, RPh, President, PerformRx; and Debra Gordon, MS

In October 2011, the Centers for Medicare & Medicaid Services (CMS) is scheduled to announce the 2012 star ratings for the nation's Medicare Advantage and Part D Prescription Drug Plans (PDPs). At this time, nothing can be done to change a plan's 2012 rating. Plans can, however, prepare for the future. Plans across the country are searching for solutions to improve their current ratings and maintain a high quality of care moving into 2013. Plans that have received the esteemed five-star rating for 2011 have been generously offering guidance to their managed care colleagues. Here are some strategic recommendations from three such plans.

Think Beneficiary First

Medicare PDPs are not yet eligible for the financial benefits Medicare Advantage Plans can garner with a high star rating. There are other benefits, however, such as the ability to register beneficiaries throughout the year. This is one reason Medco made five stars a priority, said Stephen Wogen, Vice President of Medco's Retiree Solutions. In 2011, Medco's Retiree Solutions became the only national PDP to earn five stars. Since Medco doesn't invest much in advertising, Wogen said, the five-star rating is invaluable in recruiting and maintaining members.

To garner the high rating, Medco focused first on the beneficiary, he said. That means identifying and proactively addressing potential "pain points" that could hurt ratings on the customer service side. For instance, when the company noticed many complaints came from members who learned they had hit the coverage gap while filling a prescription at the pharmacy, Medco began communicating with members as they approached the gap. The printed and Web-based communication plan Medco developed not only reminds beneficiaries that the gap is imminent, but recommends lower-cost, generic alternatives for those using branded drugs and highlights the cost-savings potential of mail-order medications.

Medco used the same proactive approach as it consolidated plans in certain regions by providing 24/7 access to member service representatives. "The reps address questions to help the beneficiary understand what's changing in the benefit, the new-versus-old price, and to help optimize the new benefit decision process," Wogen explained. The investment is worth it, he said. "The majority of complaints come in January, so we make a very focused effort to make sure they do not come from our members. If you get it right on day one, you will have very happy beneficiaries."

To garner its five-star rating in customer service—up from historically low ratings of one or two—Medco consolidated its Medicare customer service departments into a single dedicated business unit and focused on training staff to appropriately communicate with an elderly population. That involved a Medicare 101 training program for every call center representative. Those who staff the medication therapy management (MTM) call center must also undergo senior sensitivity training, a se-

Mesfin Tegenu, MS, RPh

ries of hands-on exercises and sensory perception education designed to mimic the physical challenges older individuals face. This has paid off; in 2011, the company's complaint rate was 0.06 per 1,000 members, down from 0.35 in 2010.

Customer service is just one focus, however. "We have more than 300 metrics that we monitor on a weekly or monthly basis," Wogen said, with subsets geared specifically toward the star ratings. This year, the company also launched a "Keep the 5 Alive" campaign to maintain its rating and keep employees energized.

In addition, "everyone who touches Medicare business at Medco has to go through a formal certification based on online tools and evaluations and training," he said. If they don't pass the training, they are pulled off the Medicare business.

Why so much effort for no increase in reimbursement? Wogen figures it's only a matter of time before pharmacy benefit managers (PBMs) receive bonuses based on their star ratings.

Honing In on Quality

By the time the criteria for the first round of star ratings were announced, Blue Cross and Blue Shield Northern Plains Alliance Vice President and CEO Deborah B. Madson said there was little the company could do except hang on and hope its current programs and culture could meet the requirements. It seemed to be enough, since the company's MedicareBlue Rx, the Part D benefit for Medicare plans in seven Midwestern states, garnered a perfect score in 2011, one of only four Part D plans to do so.[1]

The five stars affirmed that "we are directionally correct and consistent," said Madson. Now, with more specifics in the criteria and more time to prepare, "we have a much greater chance to proactively enhance any of the approaches we've taken so far so that we can stay on track," she said.

But, she notes, "For me to say that we're always in control of what our rating is would be an overstatement." For instance, the plan contracts with a PBM to manage drug distribution. Thus, the plan loses control over large aspects of the customer experience. "At any one time, someone can have a bad experience with the pharmacy and, even if it was appropriate, that can lead to a less-than-positive experience" that appears in the Consumer Assessment of Healthcare Provider and Systems (CAHPS) survey, she said.

To address that issue, Madson said the company is considering how to incorporate star rating criteria into its PBM contract. That will take time, however, and needs to be done "with a carrot, not a stick ... in a thoughtful, productive, quality-improvement method that always keeps the beneficiary at the forefront of our thinking."

Although working to incorporate star rating criteria into existing PBM contracts is a promising idea, there are existing examples of PBMs that are working proactively to help their customers achieve five stars. For instance, PerformRx, LLC, uses a systematic, measured, and unified approach to replicate CMS star rating methodology, identifying and correcting low-performing measures and assisting in maintaining high-rated measures. PerformRx also uses its own proprietary technology to enhance plans' MTM services. In addition, it offers an enhanced member complaint resolution process to improve the overall member experience and ensure higher CAHPS scores. Other opportunities for PBMs to assist their customers in achieving high star ratings include monitoring call centers to meet CMS requirements for hold times, disconnect rates, call answer time, and information accuracy; ensuring that drug prices submitted to CMS are accurate; and developing and reviewing reports to enhance patient safety.

In the end, Madson said, "there is no rocket science" to getting five stars. "This is just putting in the hard work, meeting the government's expectations, being vigilant on a day-to-day basis with all the governmental/contractual obligations we need to fulfill and, perhaps most importantly, focusing on member-based issues."

From the Health Plan Perspective

When Kaiser Permanente's Colorado and Hawaii Medicare Advantage plans received five stars each in the pharmacy categories, as well as the inaugural Pharmacy Quality Alliance (PQA) Quality Award for their rating, Richard Wagner, Director of Pharmacy at Kaiser Permanente-California, wasn't surprised. That is simply what is expected from a highly integrated system like Kaiser Permanente.

"I don't want to take away the hard work that people have done to make it work in real life, but when you put the systems technology we have together with the organized delivery system Kaiser brings to the marketplace, we are well-equipped to deal with quality issues," he said. Indeed, Wagner wonders how any health plan that isn't vertically integrated can garner five stars.

"The task is daunting to make these changes if you're not integrated," he said. "Our competitors are equally smart and talented and concerned about the patients, but when it comes to operationalizing and implementing the requirements, there are some real challenges. Without the level of integration we have, it just won't be as seamless."

Still, some of the steps Kaiser takes can be duplicated even by non-integrated plans. For instance, one criterion for Medicare Advantage Plans is member falls, so reducing that risk is critical. Because so many medications can cause dizziness in elderly populations, Kaiser monitors member prescriptions and flags any considered unsafe or particularly risky in the elderly. The patient's doctor receives the list and is encouraged to consider other options. The key, Wagner said, is making the process as easy as possible for the doctor. "So much of what happens that affects the star rating occurs in the doctor's office," he said. "So you have to start there."

Room for Improvement

Within every plan there is always room for improvement regarding the quality of care provided to patients. The Kaiser Family Foundation estimated that just one in four Medicare Advantage enrollees was a beneficiary of plans that received a four- or five-star rating in 2011.[2] The plans that are able to achieve this high standard of quality will enjoy the benefits of continuous eligibility and financial rewards as stipulated by the federal reform legislation.[3] To get to five, however, plans need to focus both internally and externally: internally on the quality of their employees and the robustness of their information systems, and externally on the beneficiary.

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Medicare Part D Prescription Drug Plan Star Rating Performance Metrics[4]

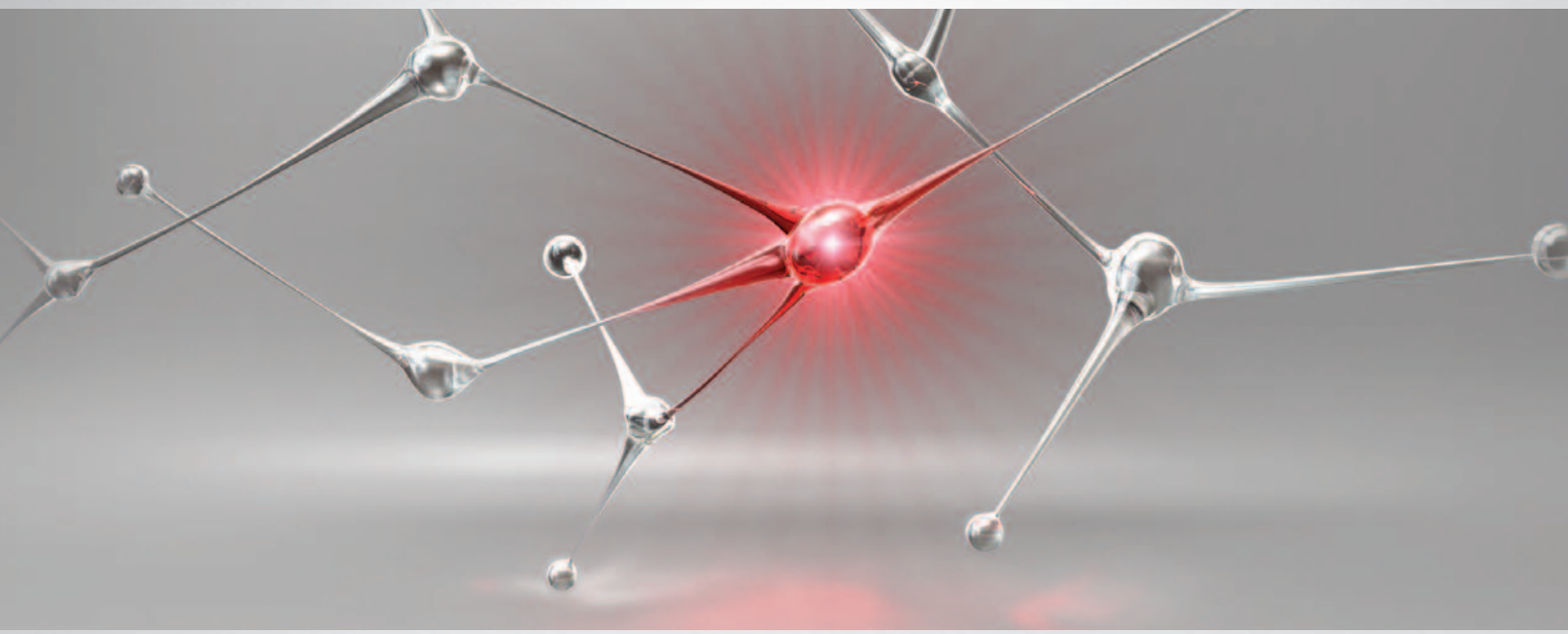
Drug Plan Customer Service (Seven Measures)
- Time on hold when customer calls drug plan (minutes: seconds)
- Time on hold when pharmacist calls drug plan (minutes: seconds)
- Accuracy of information members get when they call the drug plan
- Drug plan provides pharmacist with up-to-date and complete enrollment information about plan members
- Drug plan's timeliness in giving a decision for members who make an appeal
- Fairness of drug plan's denials to a member's appeal, based on an independent reviewer
- Availability of TTY/TDD services and foreign language interpretation when members call the drug plan

Member Complaints and Staying with Drug Plan (Five Measures)
- Beneficiary access problems Medicare found during an audit of the plan
- Complaints by members about joining and leaving the drug plan (rate per 1,000 members)
- All other complaints about the drug plan (per 1,000 members)

Member Experience with Drug Plan (Three Measures)
- Drug plan provides information or help when members need it
- Members' overall rating of drug plan
- Members' ability to get prescriptions filled easily when using the drug plan

Drug Pricing and Patient Safety (Four Measures)
- Completeness of the drug plan's information on members who need extra help
- Drug plan provides accurate price information for Medicare's Plan Finder website and keeps drug prices stable during the year
- Drug plan's members 65 and older who received prescriptions for certain drugs with a high risk of side effects, when safer drug choices may be possible
- Using the appropriate blood pressure medication recommended for people with diabetes

Astellas Health Systems: A Convergence of Innovative Therapy and Service



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A Convergence of Innovative Therapy and Service

Overactive Bladder

Overactive bladder (OAB) is a common condition in which one experiences urinary urgency and/or urinary incontinence.[1-4] It is a detrimental illness that affects more than 30 million people in the U.S. alone, resulting in continually escalating healthcare costs.[1,2] These expenditures aren't solely attributed to healthcare utilization, such as physician office visits and prescription medications. Indirect OAB costs, including disruption of workflow and reduced productivity, also result in a significant financial impact on the U.S. economy.[1] As seen in Figure 1, there are many different categories of OAB spending. These costs can also include those related to the treatment of OAB-related consequences, such as urinary tract infections (UTIs), skin infections, falls, and fractures.[1]

Although pharmaceutical agents are currently the foundation of OAB therapy, medication costs represent a relatively small portion of total OAB expenditure. The financial burden is largely derived from the utilization of outpatient services.[1] It was estimated that in 2007, patients with OAB averaged $1,925 in both direct and indirect costs annually.[2] This per capita cost estimate is expected to rise 2.3 percent by 2020.[2]

This increase, though seemingly minimal, will escalate the annual healthcare costs of OAB by 25 percent to a staggering $82.6 billion within the next decade (see Fig. 2, page 37). This growth can be partially attributed to the country's rapidly growing elderly population.[2]

Though many of the current costs are primarily incurred by 45- to 54-year olds, the increasing population of elderly patients will begin to place a greater emphasis on direct medical costs. The medical expenses borne by Medicare beneficiaries are about double those of the population younger than 65.[2] The shift in costs will become more evident as the U.S. demographics continue to change in the coming years.

Although OAB can be serious and debilitating, many patients are hesitant

Fig. 1 **COST BREAKDOWN OF OAB[1]**

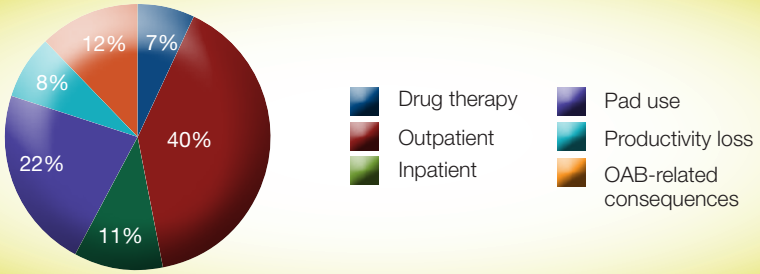
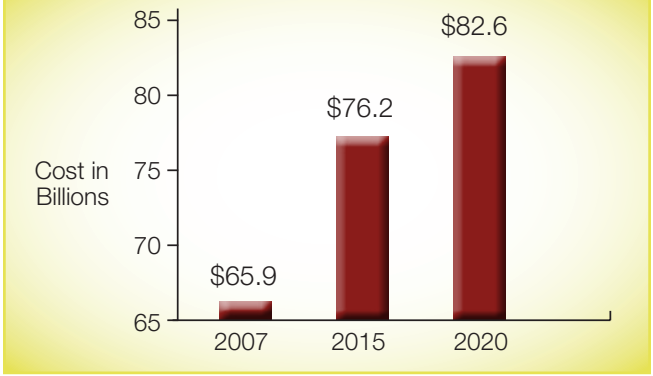


Fig. 2 **PROJECTED COSTS ASSOCIATED WITH OAB[2]**



or embarrassed to discuss the illness with their physicians. This leads to a substantial amount of undertreated, and often untreated, patients suffering from this condition. Compounding this problem is the high rate of medication discontinuation observed in this patient population. Due to bothersome side effects of generic antimuscarinics, which are regarded as the first-line therapy, adherence rates drop to as low as 38 percent after only three months of treatment.[3] After discontinuation, the majority of these patients never seek alternative therapy and remain uncontrolled, contributing to increasing indirect costs. These uncontrolled patients can trigger higher healthcare costs that otherwise could be managed with proper pharmacotherapy. Certain therapeutic treatment options, though seemingly expensive, have been associated with reduced medical expenditure in both medical and nonmedical resource utilization.[4] However, patients must remain adherent to their antimuscarinic therapy in order to observe the cost-savings potential. As it is becoming increasingly evident that OAB expenditure is on the rise, therapeutic interventions to improve patient care and increase pharmacologic adherence will be essential for both public and private health systems in the ensuing years.

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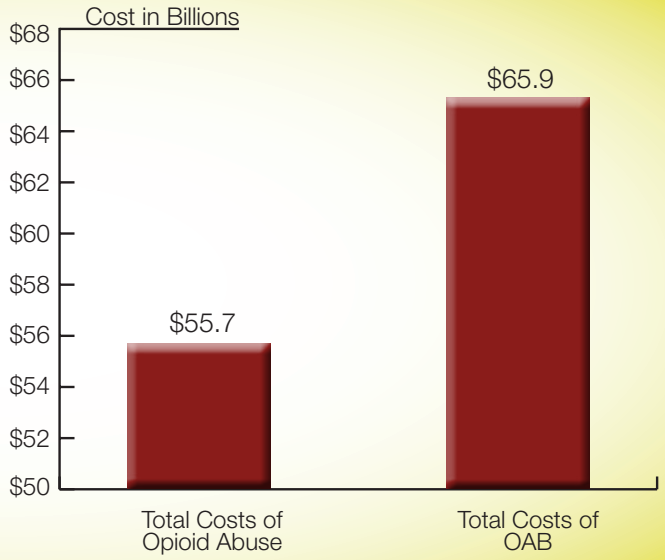
Opioid Abuse vs. OAB: Comparative Cost Analysis (2007)[2,4,5]

Similarly to OAB, opioid abuse is correlated with high medical expenses and also carries societal costs, which results in an escalating financial burden. Indirect costs for opioid abuse are derived primarily from implications to the criminal justice system and loss of productivity in the workplace.[5] In 2007, these costs escalated to an overwhelming $55.7 billion. For both OAB and opioid abuse, healthcare expenditures are only projected to increase in the next several years. Although annual costs associated with OAB exceed $65 billion, this condition has traditionally received little attention in the managed care arena, contributing to inappropriate therapy management.



The Clinical Benefits of Prior Authorizations: An Effective Tool to Improve Health Outcomes and Ensure Patient Safety

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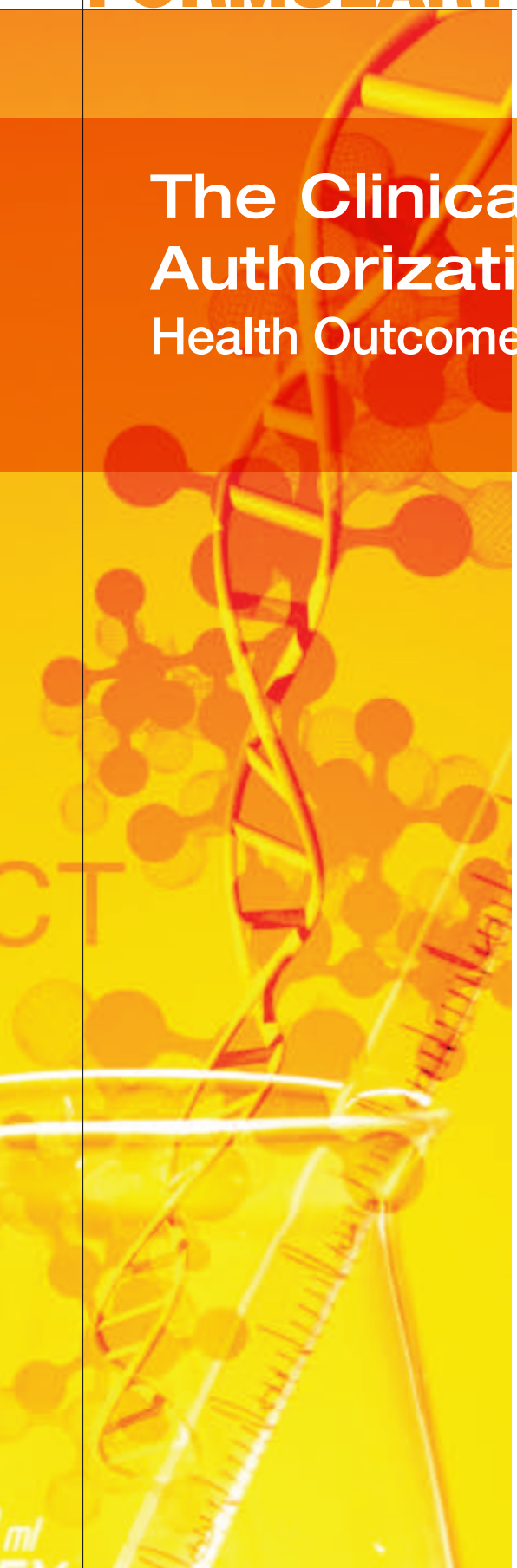

Background

In the healthcare industry, many practicing physicians and insurance plan beneficiaries perceive prior authorizations (PAs) primarily as mechanisms to reduce costs for health plans and inhibit patient access to expensive medications. While the ability of PAs to generate cost savings is well documented,[1-3] PAs are also ideally positioned to serve as strategic clinical tools that promote positive outcomes and patient well-being. When considering the potential to avoid adverse events, medication interactions, and dangerous off-label use, PAs provide an essential resource to simultaneously act in the best interest of patients and achieve the goal of reducing inappropriate prescribing practices. The key to accomplishing this goal is a comprehensive medication review system that identifies and prevents the dispensing of inappropriate therapies. The "development of clinically rational prescription drug policies,"[4] is a worthy goal for all insurers and can lead to a reduction in overall healthcare expenditure through reduced hospitalizations, drug interactions, and inappropriate prescribing.

Clinical Opportunities for PAs

There are a myriad of opportunities to more effectively manage the care of patients, and thus improve outcomes, using prior authorizations. Requiring a PA guarantees that a patient-specific therapeutic review will be conducted, not only at the provider level, but also within the health plan. The process reduces the risk of potentially fatal interactions, dangerous side effects, and suboptimal medication efficacy. One study found that administrative claims analysis could be a cost-effective strategy to monitor prescriber compliance with black-box warnings in older patients at high risk.[5] Similarly, a study on opioid dependence underscored the need for physicians, employers, and managed care organizations to work together to integrate treatment, an approach for which a PA could

Saira A. Jan, MS, PharmD

have life-saving results.[6] Injectable rheumatoid arthritis drugs, such as etanercept (Enbrel®, Amgen) and adalimumab (Humira®, Abbott), are commonly affected by PAs as a method to inspire appropriate tuberculosis screening to minimize patient risk.

Due to concerns over abuse, diversion, and the need for intensive regulation, certain therapeutic areas inherently lend themselves well to stringent management through implementation of policy controls, such as PAs. Treatment of substance abuse, particularly opioid dependence, is one such example. Many health plans have begun developing and implementing PA criteria as a method to appropriately manage patients prescribed Suboxone® (buprenorphine/naloxone, Reckitt Benckiser). Suboxone® is one of the few pharmacologic treatment options for opioid dependence that can be utilized without daily and direct physician supervision. However, implementing PA criteria against Suboxone® can satisfy a variety of clinical objectives when managing this patient population. One reason is to promote appropriate utilization. Suboxone® is only indicated for maintenance treatment of opioid dependence.[7] Many physicians, however, prescribe Suboxone® off-label for chronic pain management, an indication not currently approved by the U.S. Food and Drug Administration (FDA) and that lacks sufficient supporting evidence. Ensuring patients receive the most clinically effective treatment is an additional reason for PA implementation against Suboxone®. By establishing specific PA criteria, health plans can encourage the appropriate referral to necessary detoxification programs for many of these patients. Substance abuse is an extremely complex and chronic condition. It requires a multifaceted approach to ensure the best possible outcomes. The implementation of PA criteria against Suboxone® is one method to satisfy these clinical goals.

Off-label prescribing is also a common issue that can be addressed through proper utilization of a PA. The practice of off-label prescribing places patients at an increased risk for medication-related adverse events, since the product is being used for a condition, or in a patient population, for which it doesn't contain an approved indication. For example, Actiq® (fentanyl lozenge, Cephalon) is a short-acting opioid that is currently only indicated for acute pain associated with cancer-related diagnoses.[8] It is often subject to a PA in an attempt to curb off-label use in patients without a diagnosis of cancer-related pain, thus reducing the potential for abuse, diversion, and unnecessary drug exposure. Lovaza® (omega-3-acid ethyl esters, GlaxoSmithKline) is another example. Lovaza® is only approved at a 4-gram daily dose for the reduction of triglyceride levels,[9] yet is also used off-label at different doses for other indications, despite a lack of controlled studies showing clinical benefits outside triglyceride reduction.

OFF-LABEL USE

Atypical antipsychotics are often used off-label to treat a variety of conditions. For example, due to its sedating effects, low-dose quetiapine is frequently used off-label for insomnia.

Atypical antipsychotics are often used off-label to treat a variety of conditions. Due to its sedating effects, low-dose (25 mg) quetiapine (Seroquel®, AstraZeneca) is frequently used off-label for insomnia; this occurs despite the availability of other alternatives that carry approved indications for sleep disorders, without the potential long-term side effects of cardiac and metabolic disorders observed with quetiapine and other antipsychotics.[10] Atypicals are also frequently prescribed for elderly patients with dementia, despite black-box warnings indicating increased risk of death when used for this purpose. A February 2010 study[11] analyzing data from the 2004 National Nursing Home Study (NNHS) found that 86.3 percent of elderly nursing home residents prescribed atypical antipsychotics were receiving them for off-label uses. A report[12] issued in May 2011 by the Office of

Inspector General, U.S. Department of Health & Human Services, offered similar results, indicating that 95 percent of atypical antipsychotic use in elderly nursing home residents was for either off-label use or in patients for whom the black-box warning would be applicable. Despite ongoing controversy, this issue remains an example of a situation in which a PA would be well-suited to ensure appropriate prescribing and avoidance of unnecessary adverse events and medication risk.

PAs can also be used to address the limitations of studies associated with a specific drug's FDA approval process, such as the way pharmaceutical companies design clinical trials. Many new product approvals are based on studies conducted against placebo comparators in highly controlled environments and exclude high-risk populations with serious comorbidities; this can be problematic for extrapolation to everyday clinical practice, as many real-world patients, particularly those with chronic diseases, present as complex cases with numerous comorbid diagnoses. For example, the trials for rosiglitazone (Avandia®, GlaxoSmithKline) and pioglitazone (Actos®, Takeda) did not include many patients with congestive heart failure (CHF),[13] despite the fact that diabetes and CHF are fairly common comorbid diagnoses.[14] During post-marketing evaluation, however, these medications were found to be associated with a worsening of CHF and other cardiovascular problems.[15] Varenicline (Chantix®, Pfizer) is an oral smoking cessation medication that has been linked with increased suicide risk during post-marketing analysis.[16] Smokers commonly present with various psychiatric concerns that may predispose them to suicidal behavior, yet many pivotal studies that led to the drug's approval excluded smokers with comorbid psychiatric conditions.[17] Due to a variety of factors, prescribers may not always have all of the current or critical information they need to ensure both safe and effective medication utilization. Prior authorizations can assist prescribers in making more informed decisions for their specific patient populations and sub-populations, and allow them to more confidently provide treatment, by imparting a control mechanism that consistently stays abreast of the latest clinical developments and provides frequent and timely feedback as to the appropriateness of current therapy.

It is imperative that PA criteria are reviewed regularly to ensure consistent clinical relevance and to address critical advancements in the field.

The Need for Continued Analysis: Three Recent Examples

Due to the fluctuating dynamics of the healthcare system and the frequent updates to prescribing practices, evidence-based guidelines, and medication safety data, it is imperative that PA criteria are reviewed regularly to ensure consistent clinical relevance and to address critical advancements in the field. This is evidenced by recent developments, such as updated labeling and prescribing information for many commonly-used medications. Consider Avastin® (bevacizumab, Genentech), the world's largest-selling cancer drug. In June 2011, an FDA advisory panel ruled that the medication should no longer be used in breast cancer patients. The evidence concluded that Avastin® was unsafe and ineffective for treating breast cancer.[18] Despite the current controversy swirling around this topic, it serves as an effective illustration of the potential opportunity for PA application.

Two additional key recommendations issued by the FDA in June 2011 illustrate areas of potential need for clinically-sound PA procedures. FDA officials modified their prescribing recommendations for patients with chronic kidney disease (CKD), recommending more conservative dosing of erythropoiesis-stimulating agents due to continued safety concerns based on data showing increased risk of cardiovascular problems.[19] Controlled trials found greater risk for adverse cardiac events and stroke among patients with chronic kidney disease when ESAs were given to target a hemoglobin level of greater than 11 g/dL.[20] The FDA issued a similar safety

communication regarding simvastatin, which included recommendations to limit use of the 80 mg dose, as well as requirements to amend the product label to specifically include new contraindications and dose limitations when used with certain medications. It is now recommended that new patients should not be started on simvastatin 80 mg, and patients should be maintained on 80 mg only if they have been treated with that dose for at least 12 months without evidence of muscle toxicity.[21] These examples are important in that they link scientific data with adverse outcomes to medications within precise patient populations, allowing payors to "connect the dots" and implement PA policies to reduce potentially inappropriate prescribing, and, most importantly, protect patient safety.

Concerns and Misconceptions

There are warranted concerns that PAs could hinder access to care,[22] yet research has shown the process does not construct such a barrier if implemented correctly. Particularly in the realm of chronic disease management, PAs have proven to be effective clinical strategies that provide greater quality of care for patients without placing an undue onus on the patient or provider. For example, a study of the impact of PAs for asthma medications on the utilization of emergency health services found no impact on first asthma-related hospitalization or emergency department visits after implementation of the PA for medications combining inhaled corticosteroids and long-acting bronchodilators.[23] In diabetic patients, PAs have been associated with increased rates of HbA_{1c} testing, thus leading to enhanced positive outcomes.[24] After implementing the PA policy, 100 percent of patients identified through the program received HbA_{1C} testing, a rate that dropped to about 86 percent when the policy was rescinded.[24] While some make the argument that PAs can impede care, observational studies such as this demonstrate the ability of PAs to facilitate improvements in patient care.

A common misconception is that all PAs take a "one-size-fits-all" approach to managing specific products and are measured solely based on their ability to reduce spending on high-cost medications. In reality, there is evidence to suggest that the success of a PA hinges on many criteria.[25] Structure, implementation, and actual operational logistics are vital components of a PA policy that may vary widely, thus generating results that differ dramatically from one organization to another. This is often true even when comparing policies that have been enacted to manage the same medication or therapy class. This is illustrated in a study that examined different step-therapy programs for COX-2 inhibitors in two Canadian provinces from January 1996 to November 2002. A more restrictive program that designated COX-2 inhibitors, including rofecoxib (Vioxx®, Merck, withdrawn from the market in 2004) and valdecoxib (Bextra®, Pfizer, withdrawn from the market in 2005) as fourth-line treatment after NSAIDs found no increase in hospital admissions, whereas the comparator with a less intensive step-therapy intervention experienced a 16 percent increase in hospital admissions related to gastrointestinal hemorrhage.[26] Though not the focus of the study, it is also possible that the adverse cardiovascular profiles of rofecoxib and valdecoxib may have contributed to increased costs of care and negative outcomes for patients. This study demonstrates that differences in policy design can account for markedly differing results, while affirming the notion that programs designed to limit medication use to populations in which they are most likely to have a benefit can promote patient safety.

Looking Ahead

Although PAs have proven effective in preventing inappropriate prescriptions, reducing cost-prohibitive treatments, and addressing potential problems with patient compliance, they may not be appropriate in all situations.

Prior Authorizations and Diabetes

In diabetic patients, PAs have been associated with increased rates of HbA_{1c} testing, thus leading to enhanced positive outcomes.

Some of the same studies showing positive clinical outcomes associated with using a PA also raised concerns about unintended effects on treatment initiation and medication changes.[27] What is warranted is a comprehensive approach, more study into clinical outcomes,[28] and flexibility when new research uncovers utilization patterns or other information to help inform denial processes.

Taken from a broader perspective, a PA is appropriate also in light of the long-term consequences of chronic medications. If a chronic medication is not providing a benefit, a PA is an excellent mechanism by which to reevaluate its effectiveness, or lack thereof. If a PA limits a prescription to six months or a year, the mechanism will ensure a renewed analysis of the patient's need for that medication. Otherwise, that patient may simply continue refilling a prescription with no guarantee of safety or efficacy.

It's important for managed care organizations to not only document reasons for medication denials, but also regularly review denial reports. This allows for ongoing evaluation of the benefits offered by the PA, as well as monitoring of the overall outcomes. The reasons for denial should also be circulated to physicians and members. The positive result will be threefold: educating physicians on considerations when prescribing particular medications; illustrating why a PA is an essential tool for improved clinical outcomes; and helping the healthcare industry provide better overall education on appropriate use of prescription medications.

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Common Reasons for Denial

PA requests can be denied for a variety of reasons but are generally aimed at protecting patients and ensuring appropriate treatment. In fact, all PA policies are developed by a group of internal and external physicians who review the clinical literature and determine the stipulations for approval; these criteria cover all FDA-labeled indications, and also provide coverage for off-label use when there is sufficient evidence to support the indication. In this way, the PA process can essentially be considered a medical necessity evaluation. Despite this, many patients and physicians maintain the belief that PAs are merely a managed care cost-containment tool. This is understandable, however, because the drugs used to treat complex conditions often are the most expensive. Consider, though, some of the clinical reasons for medication denials:

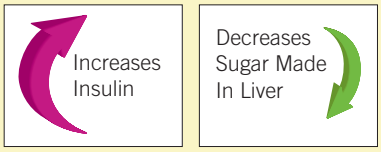
- **Lovaza®:** Patient has a triglyceride level that is not equal to or greater than 500 mg/dL; request is for more than four capsules per day; patient age is less than 18.
- **Revatio®:** Patient is on nitrate therapy or the requested dose exceeds 20 mg TID.
- **Sancuso®:** Patient's ability to use oral anti-nausea medication
- **Lotronex®:** Patient is male, or other "anatomical or biochemical abnormalities of the gastrointestinal tract have not been excluded as a cause of the symptoms."
- **Xifaxan®:** Request is for more than 550 mg twice daily.
- **Zithromax®:** Request is for an oral antibiotic for more than one month in duration.
- **Byetta®:** Pancreatitis
- **Sutent®:** No coverage for the treatment of pancreatic cancer
- **Tarceva®:** No coverage for locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen
- **Temodar®:** No coverage for sarcoma
- **Namenda®:** Patient does not have diagnosis of Alzheimer's disease. Request is for memory loss or migraine headache.
- **Stimulants:** Requests to treat MDD, idiopathic edema, chronic fatigue, and malaise
- **Aricept®:** Request is for unspecified dementia, traumatic brain injury, ADHD, depression, or no diagnosis of Alzheimer's disease.
- **Celebrex®:** Patient does not have a documented contraindication to or a potential drug interaction with a generic NSAID.
- **Phentermine:** No weight loss after four weeks of therapy
- **Enbrel® and Humira®:** Active infection or no record of tuberculosis screening
- **Growth hormone:** Use in anti-aging clinics
- **Aranesp®, Epogen®, Procrit®:** Patient does not have hemoglobin of 11-12 g/dL or hematocrit of 33-36 percent; request is for more than one injection of Aranesp every 14 days or if the patient is not currently taking or receiving iron supplementation; patient has had 12 weeks of therapy, response was not achieved; Procrit for the treatment of a diagnosis of anemia, unspecified; Procrit if the patient does not have a glomerular filtration rate (GFR) of less than 60 mL/min.

MERCK

Today, I took steps to balance my TYPE 2 DIABETES.

Today, I chose a balanced diet and talked to my doctor.

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.

Kidney problems, sometimes requiring dialysis, have been reported.

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 Helps™ 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
- kidney problems

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 happened 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.
- **Kidney problems,** sometimes requiring dialysis

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.

Revised April 2011

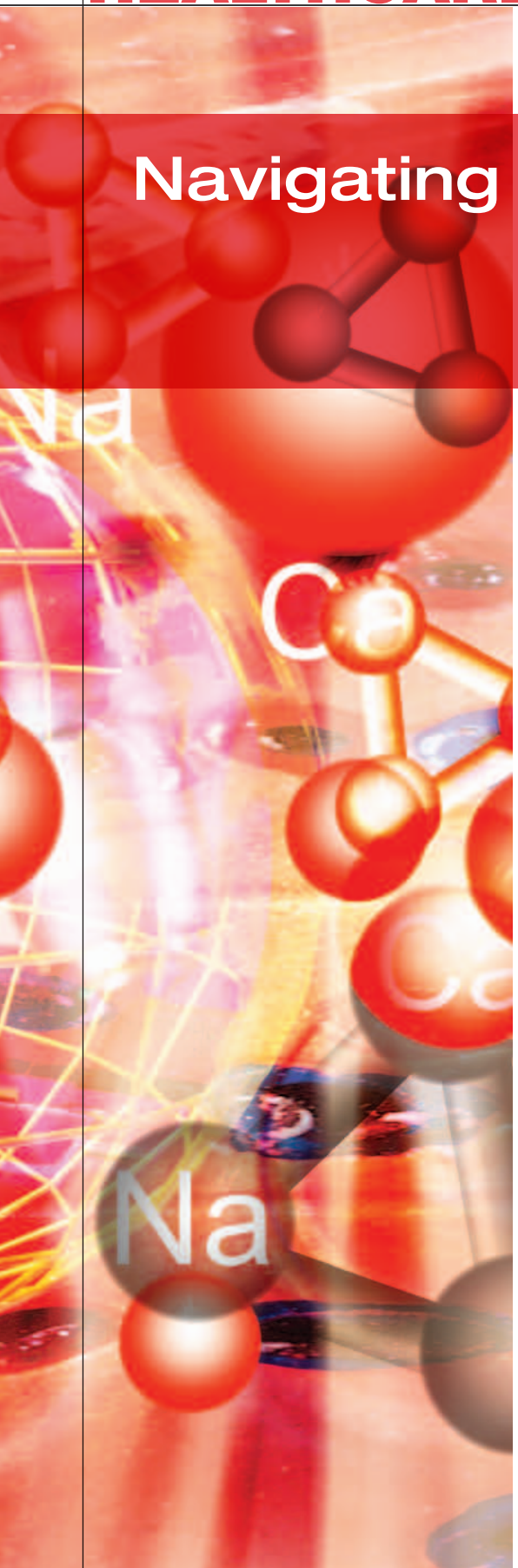
Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy
9984404
US Patent No.: 6,699,871

Januvia® (sitagliptin) tablets

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

DIAB-1008452-0000



Navigating Accountable Care Organizations (ACOs)

Eric Cannon, PharmD, FAMCP, Director of Pharmacy Services, Director of Health and Wellness, SelectHealth

Aligning financial, professional, and regulatory incentives with the goals of improved health outcomes through higher quality of care and lower costs are the chief principles of accountable care organizations (ACOs). In theory, following and achieving these values through an integrated healthcare structure will positively address the clinical and financial limitations within the current fragmented delivery system.

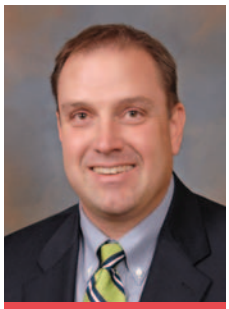
The recent healthcare reform legislation is inspiring health systems to adopt the ACO structural model. The U.S. government is now offering several strategic options to support payor participation. Due to ACO-related reimbursement parameters, the importance of adhering to essential population health management tools, providing a payment structure that allows for risk-based adjustments when necessary, and developing initiatives designed to improve care is becoming increasingly evident.

The principal question in the managed care arena involves the true cost-effectiveness of transitioning to an ACO model. The actual effect ACOs will have on reimbursement has been a controversial topic for the past 18 months and remains to be fully understood. Thus far the ACO reimbursement system outlined in the Patient Protection and Affordable Care Act (PPACA) is structured upon care provided for Medicare fee-for-service beneficiaries, with providers receiving Part A and B payments. When ACOs meet predefined economic targets as well as quality standards, the ACO and federal government are aligned to share in the resultant savings.

Questions About Reward System

Some questions remaining in the ACO reimbursement environment include how organizations will be rewarded for managing care and how those rewards will be distributed. Eventually, periodic payments will be set, resulting in per-patient dollar amounts that vary according to health status, age, and other factors. In the meantime, organizations have been able to prepare for the ensuing changes by keeping abreast of the ways federal healthcare reform is shaping the ACO environment.

In April, the Centers for Medicare & Medicaid Services (CMS) issued a proposed rule to implement the Medicare Shared Savings Program.[1] In this program,



Eric Cannon, PharmD, FAMCP

providers can assimilate into ACOs for service integration and participate in the reimbursement incentives offered by Medicare. While the ACO model is appropriate for patients across their lifespan, the Medicare population is a federal target for many reasons. The two most compelling reasons are (1) the federal government is ultimately responsible for the healthcare costs in this population and (2) more than half of today's Medicare beneficiaries have five or more chronic conditions.[2] High utilization disease states such as arthritis, hypertension, kidney disease, and diabetes take a drastic toll on the U.S. economy, especially in this patient population. Failing to coordinate the care of these patients can lead to unnecessary resource utilization, payment fraud, and deadly medical errors, all of which place an unacceptable financial burden on the healthcare system. The PPACA requires CMS to establish the Medicare Shared Saving Program no later than January 1, 2012, and it will apply only to fee-for-service beneficiaries.

Three CMS Initiatives

Three other CMS initiatives under the agency's new Center for Medicare and Medicaid Innovation illustrate the emphasis the federal government is placing on coordinated care, payment, and quality measurement. These initiatives are essentially designed to encourage providers to develop, or assimilate into, an ACO operating structure.

In May 2011, CMS published a request for applications for the Pioneer Accountable Care Organization Model. The agency describes this initiative as one "designed to test the movement of organizations experienced in providing coordinated care across settings more rapidly to population-based payment arrangements and to work in coordination with private payors in order to achieve cost savings and improve quality across the ACO, thus improving health outcomes for Medicare beneficiaries."[3] CMS is encouraging highly experienced provider organizations to participate by offering them financial sharing incentives based on high-value care. These organizations are also being persuaded by CMS to invest in infrastructure enhancements and standardization of care processes.

5,000

A common figure for what constitutes sufficient size in patient populations for a successful ACO structure. Yet many believe a more accurate minimum is at least three times this number.

One key aspect to watch will be program monitoring. CMS has plans to routinely analyze data on service utilization and "may investigate utilization patterns through comparison surveys of beneficiaries aligned with the ACO and those in the general beneficiary population, medical record audits, or other means."[4] The agency also plans to look for any systematic differences in health care between ACO patients and those not currently enrolled in an ACO model.

A second proposal that has emerged from the Center for Medicare and Medicaid Innovation is the Advance Payment ACO Initiative. This would allow particular ACOs participating in the Medicare Shared Savings Program to have access to a portion of their shared savings during the developmental stages rather than after-program analysis. This may be one of the more essential tools in promoting the transition to an ACO structure for those providers who currently lack sufficient infrastructure and staff to allow for care coordination. As of late summer 2011, CMS was still calling the proposal a "potential effort" and stipulating that care organizations themselves would be required to draft a blueprint on how the funds would be used to expand care coordination and meet the specific criteria of an ACO.[5]

Accelerated Development Learning Sessions are a third initiative CMS is utilizing as an ACO expansion tool. They have been built around a focused curriculum on core ACO development competencies: improving quality care delivery to reduce costs and increase quality, effectively using health information technology and data resources, and building capacity to manage and assume financial risk. While participation in the sessions will not factor into the official decision on whether an organization will be selected for a CMS ACO program, the regional sessions no doubt would add credence to efforts in that direction.

Successful Implementation of the Model

Organizations have been able to successfully implement the ACO model by recognizing the need for coordinated care and understanding that the ACO model establishes a spending benchmark designed around expected financial outlay. ACOs that can achieve quality targets while slowing spending growth will benefit from shared savings from payors. An example is Medicare's Physician Group Practice, a design that has resulted in significant quality and savings improvements for several large group practices.

In January, the Engleberg Center for Health Care Reform at The Dartmouth Institute helped design an ACO Toolkit, now available from the ACO Learning Network.[6] The toolkit outlines the seven key design features important to any ACO model, regardless of specific organizational structure. One frequently overlooked feature is local accountability, an important aspect necessary to improve patient health and overall care while simultaneously reducing out-of-pocket expenses in the community. In light of the importance of population health underscored in the federal healthcare reform legislation, the local accountability aspect cannot be underemphasized.

Every ACO should give providers true opportunity to access the savings that result from delivering higher-value care.

An appropriate legal structure is also important, including a governing board that is responsible for assessing and improving performance, both in the quality and financial arenas.

Another key feature that may sometimes be obscured in the larger accountable care conversation is the focus on primary care. Each ACO patient population must be identified against the backdrop of the patients' use of outpatient evaluation and management services with priority given to primary care.

There is much debate over what constitutes sufficient size in patient populations for a successful ACO structure. A common figure is 5,000, yet many believe a more accurate minimum is at least three times this number. Without a sufficient patient population, utilization measurements can easily be skewed, and care progress cannot be accurately assessed.

Unfortunately, an ACO will not arise simply out of organizational intent. Investments in delivery system improvement, such as implementing quantifiable and meaningful reforms in patient engagement, care delivery, and other areas of health, are vital to improving outcomes and costs with credibility. Shared savings are also of utmost importance. Every ACO should give providers true opportunity to access the savings that result from delivering higher-value care. CMS is currently reviewing strategies to efficiently transition from the volume-driven model, and is seeking guidance from industry leaders regarding what interventions have demonstrated success. Performance measurement, with transparent results, is an additional component necessary to facilitate ACO functionality. Such measurement should provide evidence of both cost and health impacts, and the results should be accessible to all stakeholders, including patients. The ACO Toolkit distributed by the Accountable Care Organization Learning Network proposes a set of standard ACO measures based on administrative claims data and recommends expanding performance measurement to be based on clinical and other data sources over time.[7]

An example of a functional continuum of care is Atrius Health. Atrius Health, located in Massachusetts, was founded in 2004 upon the idea of delivering integrated care in a way that would benefit patients while streamlining payment delivery and providing all patients with better care coordination. The six medical groups, representing a total of 1,000 physicians and about 1 million patients, have a common thread of operating successfully in managed care. Chief Physician Executive Richard Lopez, MD, said that while the group does have a substantial amount of fee-for-service patients, the group's history of success under global payments speaks to the value of the ACO model.

Atrius is poised to apply to participate in at least one of the CMS ACO initiatives, but like many organizations with an existing ACO-like structure, the company must evaluate whether reimbursement under the program would

be beneficial. For those who are skeptical and think back to the failed healthcare reform experiment of the 1990s, Lopez is one of many to point out how far the industry has come since then. Advances in the past 20 years that have made global payments a much more palatable and realistic approach to providing care include improvements in quality-of-care measurements, such as standards and utilization tracking. Research and technology have also made assessing the degree of illness within a population much more realistic. Information technology has gone far beyond the electronic medical record to assist in all types of care, payment, service delivery, and assessment monitoring.

Intermountain Healthcare is a not-for-profit healthcare system with more than 800 multispecialty physicians and caregivers, 23 hospitals, and 165 clinics. The development of the system's affiliated health insurance plan—SelectHealth—has allowed the organization to enhance care as well as operate with a patient base fitting to the ACO structure.

Health Management Tools

Every organization considering adopting an ACO model or integrating its existing structure into such a format must consider the essential population health management tools. These tools serve an increasingly important role in light of federal reforms. The Care Continuum Alliance's toolkit addresses this issue with an easily understandable resource list for ACOs.[8] The list includes:

- **Health Risk Assessment:** This patient survey mathematically estimates risk, both condition-specific and global, and must use participation incentives. It is to be available to both primary care physicians and their patients. Such an assessment not only facilitates ACO structuring, but also allows for early identification of highest-risk patients.
- **Evidence-based guidelines:** These must be both easily accessible and flexible clinical summaries of the optimal approaches to variables at the organizational, provider, and community levels. Such guidelines address gaps in care and facilitate monitoring of clinical performance when made available to all care team members.
- **Health Information Technology (HIT) Data Liquidity:** As organizations become more adept in all areas of HIT, it is important to recognize the need to allow for data movement within a hub that facilitates the collection, analysis, and utilization of information at many levels. This includes those of the individual patient, the clinical work unit, and the entire organization.
- **Population Health Management Service Provider Contracting:** Some believe such contracting could provide the foundation for outsourcing some or all other population health management tools, but performance guarantees and risk-based contracting would need to be included.
- **Evaluation Methodologies:** Concurrent evaluation tools can assist ACOs in understanding outcomes and provide patient services and adjust programs to better meet population needs.

Whether directly addressing the federal definition of an ACO or striving to deliver high-quality, cost-effective care, the essential elements are to identify and implement best practices, eliminate unnecessary utilization, reduce waste, and provide extraordinary service. As service delivery, reimbursement, and participation are streamlined, ACOs must remain committed to delivering compassionate, efficient, and appropriate care.

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4. Centers for Medicare & Medicaid Services. CMS Fact Sheet. Pioneer Accountable Care Organization Model Beneficiary Protections, Data Sharing and Quality Measures. Accessed 11 July 2011 at **http://innovations.cms.gov/wp-content/uploads/2011/05/Pioneer-FSQ-05-23-2011.pdf.** **See page two**.
5. Center for Medicare & Medicaid Innovation. Accountable Care Organizations Accelerated Development Learning Program. Accessed 11 July 2011 at **https://acoregister.rti.org/index.cfm?fuseaction=dsp_agenda.**
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8. Care Continuum Alliance. Achieving Accountable Care: Essential Population Health Management Tools for ACOs. Accessed 11 July 2011 at **http://www.carecontinuum.org/pubs_guide.asp.**

PIPELINE TRENDS

NEW DRUG APPROVALS

CARDIOLOGY

Brilinta™ (ticagrelor)
AWP: $4.35/tablet
WAC: $3.62/tablet
Approved: July 20, 2011
Formulation: Tablet
Manufacturer: AstraZeneca
Indication: Brilinta™ (ticagrelor) is an oral platelet $P2Y_{12}$ antagonist indicated for the treatment of acute coronary syndrome.

CARDIOLOGY

Xarelto® (rivaroxaban)
AWP: $8.10/tablet
WAC: $6.75/tablet
Approved: July 1, 2011
Formulation: Tablet
Manufacturer: Janssen Pharmaceuticals, Inc.
Indication: Xarelto® (rivaroxaban) is an oral, once-daily, factor Xa inhibitor indicated for prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery.

INFECTIOUS DISEASE

Dificid™ (fidaxomicin)
AWP: $168.00/tablet
WAC: $140.00/tablet
Approved: May 27, 2011
Formulation: Tablet
Manufacturer: Optimer Pharmaceuticals, Inc.
Indication: Dificid™ (fidaxomicin) is a macrolide antibiotic indicated for the treatment of *Clostridium difficile*-associated diarrhea.

PULMONARY

Arcapta™ (indacaterol) Neohaler™
AWP: $6.53/capsule
WAC: $5.44/capsule
Approved: July 1, 2011
Formulation: Inhalation capsule
Manufacturer: Novartis
Indication: Arcapta™ (indacaterol) is a once-daily, long-acting beta-2-agonist (LABA) indicated for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD).

EPILEPSY

Potiga™ (ezogabine)
AWP: TBA
WAC: TBA
Approved: June 10, 2011
Formulation: Tablet
Manufacturer: Valeant Pharmaceuticals and GlaxoSmithKline
Indication: Potiga™ (ezogabine) is a first-in-class potassium channel opener indicated for adjunctive treatment of partial-onset seizures in patients ages 18 years and older.

NEW FDA-APPROVED INDICATIONS

Drug Name	Approved	New Indication
Invega® (paliperidone) extended-release tablet	April 6, 2011	Treatment of schizophrenia in adolescents (ages 12 to 17)
Lamictal® XR (lamotrigine extended-release) tablet	April 25, 2011	Conversion to monotherapy in patients ≥13 years old with partial seizures taking one anti-epileptic drug
Nexium® (esomeprazole) powder for injection	April 29, 2011	Short-term treatment of GERD with erosive esophagitis in pediatrics and adolescent patients (children >1 month old)
Lialda® (mesalamine) delayed-release tablet	July 18, 2011	Maintenance of remission in patients with ulcerative colitis
Zyclara® (imiquimod) 2.5% cream	July 19, 2011	Treatment of actinic keratoses

NEW FORMULATIONS AND DOSAGE FORMS

Drug Name	Manufacturer	Approved	Advertised Advantage
Androgel® (testosterone) 1.62% Transdermal Gel (CIII)	Abbott	April 29, 2011	Androgel® 1.62% transdermal gel is a new, higher strength that delivers 40.5mg per 2 pump actuations compared to the 50mg per four actuations provided by Androgel 1%.
Creon® (pancrelipase) 3,000 unit capsule	Abbott	June 10, 2011	This is a new infant-specific dosage available to cystic fibrosis patients with exocrine pancreatic insufficiency.
Duexis® (famotidine/ ibuprofen) 26.6mg-800mg tablet	Horizon Pharma	April 23, 2011	A combination tablet indicated for relieving the signs and symptoms of rheumatoid arthritis and osteoarthritis, while decreasing the risk of developing an upper gastro-intestinal ulcer.
Lazanda® (fentanyl) nasal spray 100mcg, 400mcg (CII)	Archimedes Development, Ltd.	June 30, 2011	Nasal spray formulation with a rapid onset of action, providing cancer patients with an effective new option in the management of breakthrough pain.
Oxecta® (oxycodone HCl) tablet (CII)	Pfizer Inc. and Acura	June 20, 2011	An abuse-resistant formulation of oxycodone immediate-release tablets.
Rectiv® (nitroglycerin) ointment	ProStrakan, Inc.	June 21, 2011	Indicated in the treatment of moderate to severe pain associated with anal fissures and fistula.

NEW FIRST-TIME GENERIC DRUG APPROVALS

Alfuzosin (Uroxatral®)
Launched: July 18, 2011

Bromfenac ophthalmic solution 0.09% (Xibrom®)
Launched: May 11, 2011

Budesonide extended-release oral capsule (Entocort® EC)
Launched: June 23, 2011

Cyclobenzaprine extended-release capsule (Amrix®)*
Launched: May 13, 2011

Exemestane tablet (Aromasin®)
Launched: April 1, 2011

Letrozole (Femara®)
Launched: April 22, 2011

Methylphenidate extended-release tablet (Concerta®)†
Launched: May 5, 2011

Levofloxacin tablet, oral solution, injection (Levaquin®)
Launched: June 20, 2011

Nitrofurantoin oral suspension 25m/5ml (Furadantin®)
Launched: May 11, 2011

Triamcinolone nasal spray (Nasacort AQ®)‡
Launched: June 15, 2011

*Mylan has 180-day exclusivity rights.
† Watson has exclusivity rights for an authorized generic through 2014.
‡Teva has 180-day exclusivity rights.

PROJECTED FIRST-TIME GENERIC ENTRY

Olanzapine (Zyprexa®, Zyprexa® Zydis®)
October 2011

Olanzapine/fluoxetine (Symbyax®)
October 2011

Atorvastatin (Lipitor®)
November 2011

Atorvastatin/amlodipine (Caduet®)
November 2011

Tazarotene (Tazorac®)
December 2011

Escitalopram (Lexapro®)
March 2012

Irbesartan (Avapro®)
March 2012

Irbesartan/HCTZ (Avalide®)
March 2012

Quetiapine (Seroquel®)
March 2012

Disclosures: The Pipeline Trends information is current as of August 2011.
Estimated dates are subject to change according to additional indications/approvals, patents, patent litigation, etc.
Information available from **www.fda.gov** and **pricerx.medispan.com.**

MEDICATION SPOTLIGHT

Rivaroxaban (Xarelto®)

Background

Thromboembolic events following orthopedic surgery generate substantial negative implications for the healthcare system. Such events are consequences of improper anticoagulation following the procedure and are associated with significant morbidity and mortality for patients. Additionally, preventable thromboembolic events place an unnecessary burden upon the healthcare industry by escalating overall treatment costs of patient care. An estimated 2 million people in the U.S. develop a venous thromboembolism (VTE) each year, with medical costs approaching well over $1 billion.[1,2] VTE is manifested by deep vein thromboses (DVTs) and pulmonary embolisms (PEs). Currently, unfractionated heparin (UFH), low molecular weight heparin (LMWH), and vitamin K antagonists such as warfarin are the primary pharmacologic agents used in the treatment and prophylaxis of thromboembolic diseases. However, these treatment options carry substantial risks and require extensive monitoring and frequent dosing modifications to ensure their safe and effective use.[2] Due to the risks associated with improper anticoagulation and the costs incurred by frequent monitoring, new agents with the ability to safely and predictably anticoagulate patients may prove to be both a clinical and financial asset within the managed care industry.

Rivaroxaban (Xarelto®) is a direct Factor Xa inhibitor. By inhibiting Factor Xa, the final common pathway of coagulation, rivaroxaban is able to inhibit the formation of thrombin from pre-thrombin, thus inhibiting the ability to clot. Rivaroxaban does not require a cofactor, such as Antithrombin III, for activity. Rivaroxaban exhibits predictable pharmacokinetics across a wide spectrum of patients and offers a flat dose response for dosages up to 40 mg. This allows for predictable anticoagulation without a need for dose adjustments and routine monitoring.[3] Since gaining FDA approval in July 2011, rivaroxaban has been perceived as a novel addition to the antithrombotic drug category.

Indications, Dosing, and Warnings/Precautions

Rivaroxaban is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing knee or hip replacement surgery. Rivaroxaban is approved for the once-daily administration of a 10 mg dose for 35 days following hip replacement and for 12 days following knee replacement surgery.[3] Rivaroxaban is currently undergoing further trials to pursue additional indications. Regulatory filings in the U.S., Europe, and Japan have been submitted seeking approval of rivaroxaban for the prevention of stroke in patients with atrial fibrillation.[4]

Rivaroxaban can cause serious and fatal bleeding and should be used with caution in pregnant women due to the potential for obstetric hemorrhage and emergent delivery. Contraindications include a hypersensitivity to rivaroxaban and active major bleeding. Caution should be used in surgical settings due to the chance of epidural or spinal hematomas, which may occur in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing spinal puncture. The most common adverse reaction is bleeding. Rivaroxaban should be avoided in patients with severe renal impairment (CrCL <30 ml/min) as well as moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). Rivaroxaban should also be used with caution in moderate renal impairment.[3]

Clinical Studies

Clinical trials have shown great promise for rivaroxaban. The RECORD (Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of DVT and PE) clinical trial program consisted of four randomized, double-blind, double-dummy, multinational studies (RECORD 1, RECORD 2, RECORD 3, and RECORD 4), which compared the efficacy and safety of oral rivaroxaban 10 mg once daily and subcutaneous enoxaparin 40 mg once daily (RECORD 1-3) or 30 mg BID (RECORD 4) for prevention of VTE in patients undergoing total hip (RECORD 1-2) or total knee (RECORD 3-4) replacement surgery.[5-8] In all four studies, the composite endpoint of DVT, nonfatal PE, and all-cause mortality was significantly lower in rivaroxaban-treated patients as compared to enoxaparin-treated patients. No significant increase in major bleeding was observed between rivaroxaban-treated patients and enoxaparin-treated patients in any of the four RECORD trials. Reduction in symptomatic VTEs was also observed, which was statistically significant in RECORDs 2 and 3.

Another trial, ROCKET AF (An Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation), studied more than 14,000 patients with atrial fibrillation. Patients in the ROCKET AF trial were considered high risk as 90 percent of them had a $CHADS_2$ score of 3 or higher, and 55 percent of patients had a history of prior stroke. The

2 MILLION

An estimated 2 million Americans develop a venous thromboembolism (VTE) each year, with medical costs approaching well over $1 billion. Preventable thromboemoblic events place an unnecessary burden upon the U.S. healthcare industry.

ROCKET AF trial compared the use of rivaroxaban 20 mg once daily (15 mg once daily in patients with baseline calculated CrCl 30–49 ml/min) to adjusted dose warfarin (target INR 2-3). Rivaroxaban was superior to warfarin for the primary efficacy endpoint, showing a 21 percent relative risk reduction (RRR) for stroke and non-CNS systemic embolism. In the intent-to-treat analysis, however, the clinical results were only substantial enough to prove non-inferiority. For the primary safety outcome, the event rate for major and non-major clinically relevant bleeding was significantly lower in the rivaroxaban group compared to warfarin. Intracranial hemorrhage occurred in 55 patients receiving rivaroxaban and 84 patients receiving warfarin ($p = 0.019$).[9,10]

Although the implications rivaroxaban will have on the prevention of stroke in atrial fibrillation patients will remain rather limited until it is approved for this indication, there are a few aspects of rivaroxaban to consider:

- Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.
- Avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.[3]
- Both the pharmacokinetic and pharmacodynamic profiles of rivaroxaban have been predictable, thus requiring no routine anticoagulation monitoring. The PK and PD of the drug also suggest that variations in patient demographics will

affect parameters minimally at most, so the need for dose adjustments is unlikely.[3]

■ Warfarin can take up to seven days before exhibiting a full effect, while the action of rivaroxaban can be seen between two to four hours after administration.[9]

Ultimately, rivaroxaban has proven superior to enoxaparin in the RECORD clinical trials of patients undergoing elective total hip or total knee replacement surgery and non-inferior to warfarin in ROCKET-AF, which studied patients with atrial fibrillation and elevated risk of stroke. Its pharmacokinetic properties make it safe, effective, and predictable in patients following orthopedic surgery.[9] The introduction of rivaroxaban to the U.S. market provides a viable therapeutic option for the prevention of thromboembolic events. Additionally, pending FDA approval, rivaroxaban may prove to be a novel treatment option for such events, in addition to stroke prevention in patients with atrial fibrillation.[4]

Table 1 — ORAL ANTICOAGULANT PHARMACOKINETICS

	Rivaroxaban (Xarelto®)[3]	Dabigatran (Pradaxa®)[14]	Warfarin (Coumadin®)[15]
Onset of Action	2-4 hours	0.5-2 hours	5 days
Site of Action	Xa	Thrombin	II, VII, IX, X
Administration	QD	BID	QD
Monitoring/Dose Adjustment	No	No	Yes
Metabolism	CYP3A4/5, CYP2J2	80% Renal, 20% Fecal	CYP2C9, CYP1A1, CYP1A2, CYP3A4
Drug Interactions	Combined P-gp and Strong CYP3A4 Inhibitors	P-gp Substrates	CYP 2C9, 1A2, and 3A4, Vitamin-K Agonists

Table 2 — RIVAROXABAN (XARELTO®)[3]

Indications	• DVT prophylaxis, which may lead to PE in patients undergoing knee or hip replacement surgery
Available Strength	• 10 mg tablet
Administration	• Orally, once daily, with or without food
Contraindications	• Hypersensitivity to Xarelto® • Active major bleeding
Adverse Reactions	• Bleeding • Fluid leakage from wound • Itching • Pain in arms or legs • Blisters • Muscle spasm
Warnings/Precautions	• Risk of bleeding • Pregnancy related hemorrhage • Spinal/epidural anesthesia or puncture (black-box warning) • Renal impairment • Hepatic impairment
Pregnancy	• Category C
Breast-Feeding	• Unknown: excreted into milk of rats
Overdose	• Specific antidote is not available • Use of activated charcoal to reduce absorption in case of overdose may be considered • Due to high plasma protein binding, rivaroxaban is not expected to be dialyzable
Pricing	Rivaroxaban is priced competitively to other anticoagulants currently on the market (see Table 3).[13]

Table 3	PHARMACOLOGIC TREATMENT OF POST-ORTHOPEDIC SURGERY DVT PROPHYLAXIS [3,11-13]					
	Rivaroxaban		Enoxaparin		Warfarin*	
Orthopedic Replacement	Hip	Knee	Hip	Knee	Hip	Knee
Dose	10 mg QD	10 mg QD	40 mg/0.4 ml SQ QD	40 mg/0.4 ml SQ QD	Based on INR	Based on INR
Duration	35 days	12 days	10 days	10 days	10-35 days	10-35 days
AWP/therapy	$283.50	$97.20	$324.70	$324.70	$67.43	$67.43
WAC/therapy	$236.25	$81.00	$259.80	$259.80	$16.02	$16.02
**Warfarin dosing variable, pricing based on 5 mg 100-count bottle.*						

Considerations for Payors

Rivaroxaban is a novel anticoagulant that offers a new oral option for DVT prophylaxis in patients undergoing knee or hip replacement. In clinical trials, it has shown superiority over enoxaparin in reduction of VTEs while exhibiting similar rates of bleeding episodes. Its once-daily oral dosing makes the drug not only convenient for the patient, but also may potentially reduce the need for home healthcare nursing and other nursing costs. The additional benefit of no routine monitoring of INR or other coagulation parameters can also produce time and cost savings for patients and payors.[5-8]

Despite advances in technology and treatment, prophylaxis of VTE, particularly after surgery, still remains a major challenge in the U.S. Patients undergoing current treatment have to endure substantial risks as well as regular monitoring, frequent dose adjustments, and an increased chance of adverse events such as bleeding.[2] With rivaroxaban now on the market, prescribers and patients have a new option to consider. The future of rivaroxaban seems bright with the chance of an additional indication for prevention of stroke in patients with atrial fibrillation. If approved for this indication, rivaroxaban may prove to be a formidable competitor in this market. With competitive pricing, proven efficacy, and ease of administration, managed care organizations may find little reason to restrict the availability of rivaroxaban for patients undergoing knee or hip replacement surgery and, potentially, atrial fibrillation in the near future.

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

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and insulin has not been studied.

CONTRAINDICATIONS: Victoza® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications]*. In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there were 7 cases of pancreatitis among Victoza®-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza® were reported as acute pancreatitis and two cases with Victoza® were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues *[see Adverse Reactions]*. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® was evaluated in a 52-week monotherapy trial and in four 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza® 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza® 1.2 mg, Victoza® 1.8 mg or placebo. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. Tables 1 and 2 summarize the adverse events reported in ≥5% of Victoza®-treated patients in the five controlled trials of 26 weeks duration or longer.

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

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

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

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6

Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N =230	Placebo + Metformin + Glimepiride N =114	Glargine + Metformin + Glimepiride N =232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4

Add-on to Metformin + Rosiglitazone		
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175
Adverse Event Term	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Decreased Appetite	9.3	1.1
Anorexia	9.0	0.0
Headache	8.2	4.6
Constipation	5.1	1.1
Fatigue	5.1	1.7

Gastrointestinal adverse events: In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. *Immunogenicity:* Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia:* In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 3). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 3: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

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

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available on request.

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

Date of Issue: January 2010
Version: 1

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

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liraglutide (rDNA origin) injection

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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.

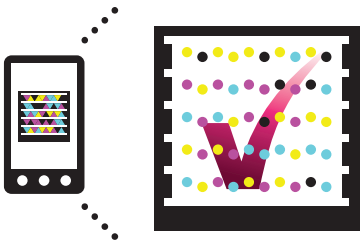
The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated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

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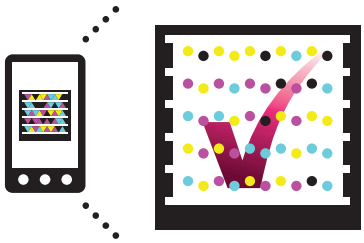

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