# Magellan Rx Report

## MEDICAL AND PHARMACY BENEFIT MANAGEMENT

## PCSK9 Inhibitors: What Can We Expect in 2015?

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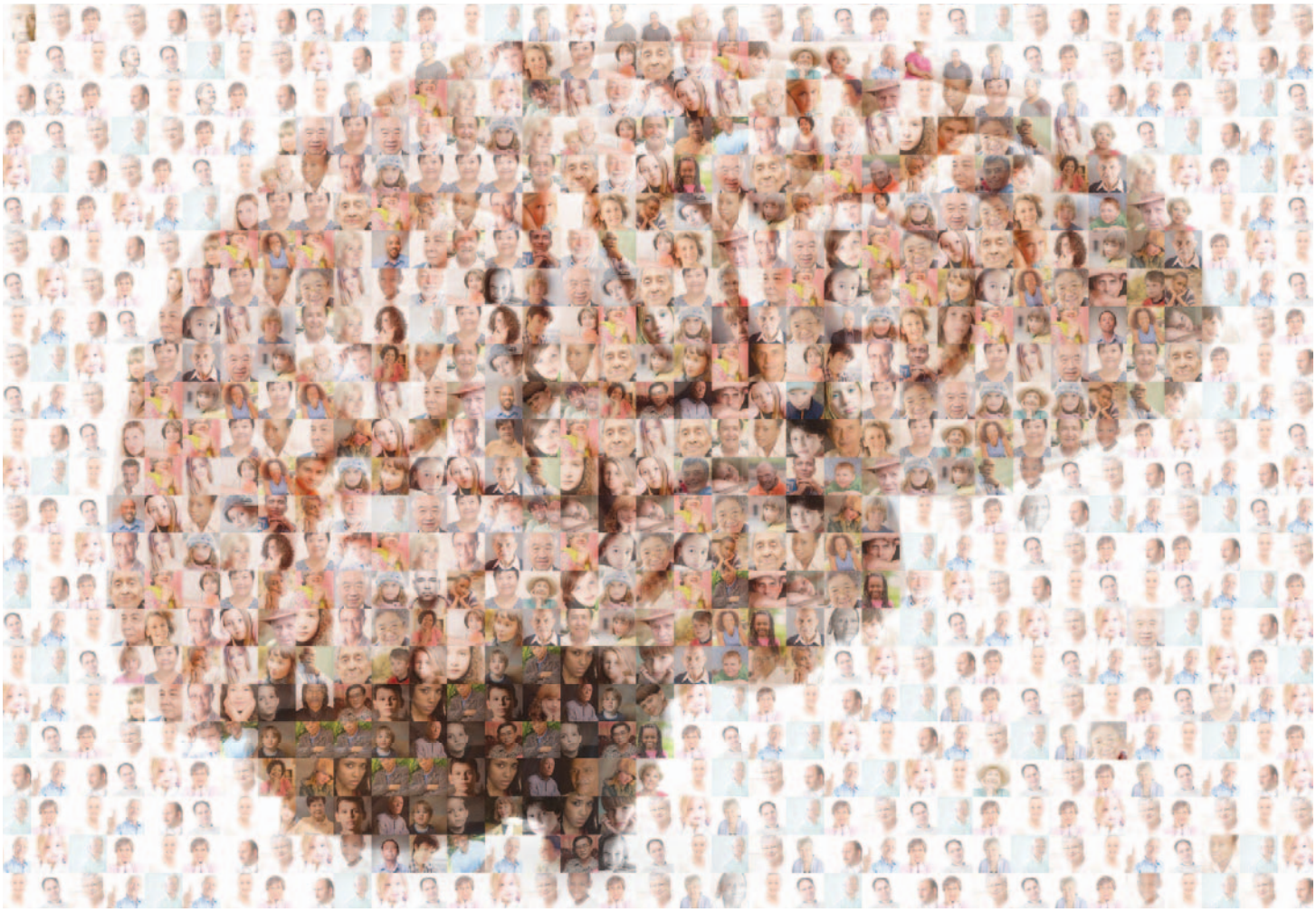
# Almost a billion people suffer from neurologic conditions worldwide.



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# WELCOME

to this issue

## features



## trends

# Letter from Magellan Rx

## Dear Managed Care Colleagues,

Susan Petrovas, RPh

With the anticipated approval of several revolutionary pharmacologic therapies, 2015 is set to be a groundbreaking year for clinical innovation in a wide variety of specialty categories. This year we are likely to witness a profound increase in hepatitis C cure rates, dramatically improved survival in difficult-to-treat cancers, and biologic therapies that will transform management approaches for traditional disease states. However, with innovation often comes increased cost. Now, more so than ever, accurate forecasting is essential to prepare for the potential economic impact associated with near-term products. The importance of this was demonstrated over the past few years by the emergence of innovative products for the management of hepatitis C. Although the extent of the associated financial impact was a surprise to most of us within managed care, some plans were more prepared than others due to the inclusion of realistic forecasting scenarios into budgetary planning. Although hepatitis C will remain a financial concern, the recent increase in the competitive landscape should help contain further price escalation.

In oncology, multiple new products are hitting the radar screen. One category is the PD-1 inhibitors. The first two competitors in this space were approved last year for the treatment of metastatic melanoma, but several more products in this category are on the horizon and are being studied in dozens of tumor types.

This year may also see a game changer in the treatment of cystic fibrosis (CF). In November, Vertex submitted the combination of Kalydeco® and lumacaftor for FDA review. Kalydeco, which costs approximately $300,000 per patient annually, is a revolutionary product in its own right, but it is only effective in a small proportion of patients with CF. The combination of these agents has shown efficacy in a much broader CF patient population and will most likely have a substantial impact on pharmacy budgets for many health plans.

These products are just the tip of the 2015 economic iceberg. However, even with the continued emergence of new and challenging financial concerns, it is important not to lose sight of our true objective: increasing quality of care and positive health outcomes for our beneficiaries. Implementing novel approaches to optimize cost-effective strategies, align medical and pharmacy benefits, and encourage clinical programs designed to improve clinical outcomes can all help promote a healthier patient population. At Magellan Rx Management, we offer integrated solutions that combine our medical, specialty, and pharmacy benefit experience, allowing us to leverage our collective scale and experience in managing total drug spending for our payor clients, while ensuring a clear focus on the specific clinical and financial needs of each individual customer.

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

Sincerely,

Susan C. Petrovas, RPh
Magellan Rx Management

# MANAGED CARE NEWSSTAND

## Costs of Treating Skin Cancer Skyrocket in the United States

The costs of treating patients with skin cancer soared five times as fast as the costs of other cancer treatments, according to researchers at the Centers for Disease Control and Prevention (CDC).

The CDC researchers evaluated the average annual costs associated with cancer treatments during two five-year time periods and found that skin cancer treatment costs rose from $3.6 billion between 2002 and 2006 to $8.1 billion from 2007 to 2011. During the same time periods, the number of adults treated for skin cancer increased from an annual average of 3.4 million to 4.9 million.

The 126 percent increase in annual skin cancer treatment costs far exceeded the 25 percent average annual increase recorded for all other cancer treatments during the study periods.

"The findings raise the alarm that not only is skin cancer a growing problem in the United States, but the costs for treating it are skyrocketing relative to other cancers," said lead author Gery Guy, PhD, of the CDC's Division of Cancer Prevention and Control, in a news release. He added that the findings demonstrate the importance of skin cancer prevention strategies.

*Source:* US skin cancer costs rise from 2002 through 2011. Centers for Disease Control and Prevention. News release. Nov. 10, 2014.

## Hepatitis C Market Heats Up: Update from AASLD

Drug companies are scrambling to gain market share in the hepatitis C virus (HCV) market, and more changes are on the horizon. Presenters at the American Association for the Study of Liver Diseases' annual meeting, The Liver Meeting®, held in November 2014, provided a preview of what's ahead.

AbbVie reported positive results with its recently approved combination of three direct-acting antivirals in specific subgroups of chronic HCV patients. A phase 2 study evaluated the effectiveness of the investigational treatment and ribavirin in patients coinfected with genotype 1 (GT1) HCV and immunodeficiency virus type 1. Researchers reported that the sustained virologic response rate (SVR(12)) was more than 93 percent at 12 weeks.

AbbVie also reported results of a phase 2 study of their investigational treatment in noncirrhotic adult liver transplant patients with recurrent GT1 HCV who were treatment naïve. The study showed that participants experienced a 97.1 percent SVR at 12 and 24 weeks after treatment.

Merck reported the interim results of a phase 2 study of its three-therapy regime (grazoprevir, elbasvir, and Gilead's sofosbuvir) in chronic HCV patients. The combination showed SVRs ranging from 80 to 94.7 percent in cirrhotic and noncirrhotic patients who underwent six and eight weeks of treatment. However, the four-week SVR (38.7 percent) was suboptimal.

Gilead released results of several studies of Harvoni®, which the FDA recently approved. Researchers completed a pooled analysis of GT1 HCV patients with compensated cirrhosis treated for 12 or 24 weeks with Harvoni alone or in combination with ribavirin. Ninety-six percent of patients achieved SVR 12. Another Gilead study evaluated GT1 HCV patients with compensated cirrhosis who failed previous therapies. Researchers found 97 percent of patients who received Harvoni alone for 24 weeks achieved SVR 12 while 96 percent of those who received Harvoni with ribavirin for 12 weeks achieved SVR 12.

Researchers from the University of Texas MD Anderson Cancer Center attempted to quantify the cost of treating all patients in the United States who have hepatitis C following the introduction of these effective but costly medications. They estimated it would cost all payors an estimated $136 billion to $188 billion to treat 1.6 million patients over the next five years. That is $65 billion more than the costs of drug therapies used before the introduction of the new direct-acting antivirals.

"The best strategy is to treat everyone," Jagpreet Chhatwal, PhD, principal investigator for the study, said in a news release. "Unfortunately, we are not seeing it happening in practice because of the cost of treatment. Either we need to reduce the price of drugs or make the best use of available resources by evidence-based prioritization."

*Sources:* Tracy S. Winners and losers at AASLD? Check out Merck, AbbVie, Gilead and J&J data. FiercePharma. Nov. 12, 2014.

AbbVie to Present Results from Studies in Chronic Hepatitis C Patients with HIV-1 Co-Infection (TURQUOISE-I) and Liver Transplant Recipients (CORAL-I) at The Liver Meeting® 2014. AbbVie. News release. Nov. 11, 2014.

Interim Data from Proof-of-Concept Study of Merck's Investigational Hepatitis C Treatment Grazoprevir/Elbasvir in Combination with a Nucleotide Inhibitor (C-SWIFT study) Presented at The Liver Meeting®. Merck. News release. Nov. 9, 2014.

Gilead Announces Harvoni Study Results in Chronic Hepatitis C Patients with Advanced Liver Disease and Those Who Failed Prior Treatment. Gilead. News release. Nov. 11, 2014.

What is the Real Cost of Treating All Patients with Hepatitis C? American Association for the Study of Liver Diseases. News release. Nov. 10, 2014.

## Orphan Drugs No Longer a Niche Market

A new report — EvaluatePharma® Orphan Drug Report 2014 — states orphan drug sales could reach $176 billion and account for 19 percent of total prescription drug sales (excluding generics) by 2020. The 11 percent growth in sales projected for orphan drugs is more than double the 5 percent growth rate the report's authors anticipate for other nongeneric drugs for larger patient populations.

Other highlights of the report include:

- In 2014, the average cost of orphan drugs per patient year was more than $137,000, while the average cost of nonorphan drugs was nearly $21,000 per patient year.
- The United States granted a record high 260 orphan drug designations in 2013.
- The development cost of phase 3 orphan drugs is lower and the anticipated return on investment for phase 3 filed orphan drugs is higher than comparable nonorphan drugs.
- The most valuable R&D drug in 2013 based on net present value was Vertex's VX-809 in combination with Kalydeco® (ivacaftor).
- The most promising orphan drug approved by the FDA in 2013 was Pharmacyclics' Imbruvica® (ibrutinib).

*Source:* New Report Shows Orphan Drug Market to Reach $176 Billion by 2020. EvaluatePharma. News release. Oct. 29, 2014.

## Sudden Rise in Generic Drug Prices Felt Throughout the Health Care System

The prices of some previously inexpensive generic medications have been rising at an unparalleled rate, according to the National Community Pharmacists Association (NCPA). Generic medications have historically been a safe and effective alternative that saved money for both patients and payors. But the NCPA notes that these sharp price hikes are "wreaking havoc" on the health care system.

Washington lawmakers investigating the issue cite disturbing examples. The price of digoxin rose from 11 cents to $1.10 per pill in less than two years. The cost of doxycycline hyclate skyrocketed from $20 a bottle in fall 2013 to nearly $1,900.

"The current situation in which unprecedented spikes in previously inexpensive generic medications are becoming commonplace is one that cannot be allowed to continue," Rob Frankil said in a NCPA news release. "These prices are wreaking havoc on patients, pharmacists and health care payors alike."

*Sources:* Pharmacist Testifies: Generic Drug Price Spikes Wreaking Havoc on Patients, Pharmacists and Health Care Payers. National Community Pharmacists Association. News release. Nov. 20, 2014.
Congressional Panel to Probe Generic Drug Price Hikes. US Senate Committee on Oversight & Government Reform. News release. Nov. 11. 2014.

## Trastuzumab Improves Outcomes for Certain Women with Early Stage Breast Cancer

Adding trastuzumab (Herceptin®) to chemotherapy regimens significantly improves outcomes for women with early stage HER2-positive breast cancer. Mayo Clinic researchers conducted a long-term study of 4,046 breast cancer patients and found the survival rate for women who received trastuzumab with chemotherapy increased by 37 percent while the 10-year overall survival rate rose from 74 percent to 84 percent.

The risk of cancer recurrences was reduced by 40 percent, and the disease-free survival rate increased from 62 to nearly 75 percent when compared with women who had chemotherapy alone.

Improvements were noted in all patient subgroups — including patients of all ages who were node-positive, node-negative, estrogen positive, and estrogen negative.

"This long follow-up of patients shows that we have really altered the natural history of this disease," lead author Edith Perez, MD, said in a news release. "Herceptin works — and it works for a long period of time."

*Source:* Perez E, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2–positive breast cancer: Planned joint analysis of overall survival From NSABP B-31 and NCCTG N9831. *J Clin Oncol.* Oct. 20, 2014. **http://jco.ascopubs.org/content/early/2014/10/14/JCO.2014.55.5730.abstract.**

# PCSK9 Inhibitors: Impact on the U.S. Health Care System

*Matthew Mitchell, PharmD, MBA, Director, Pharmacy Services, SelectHealth*

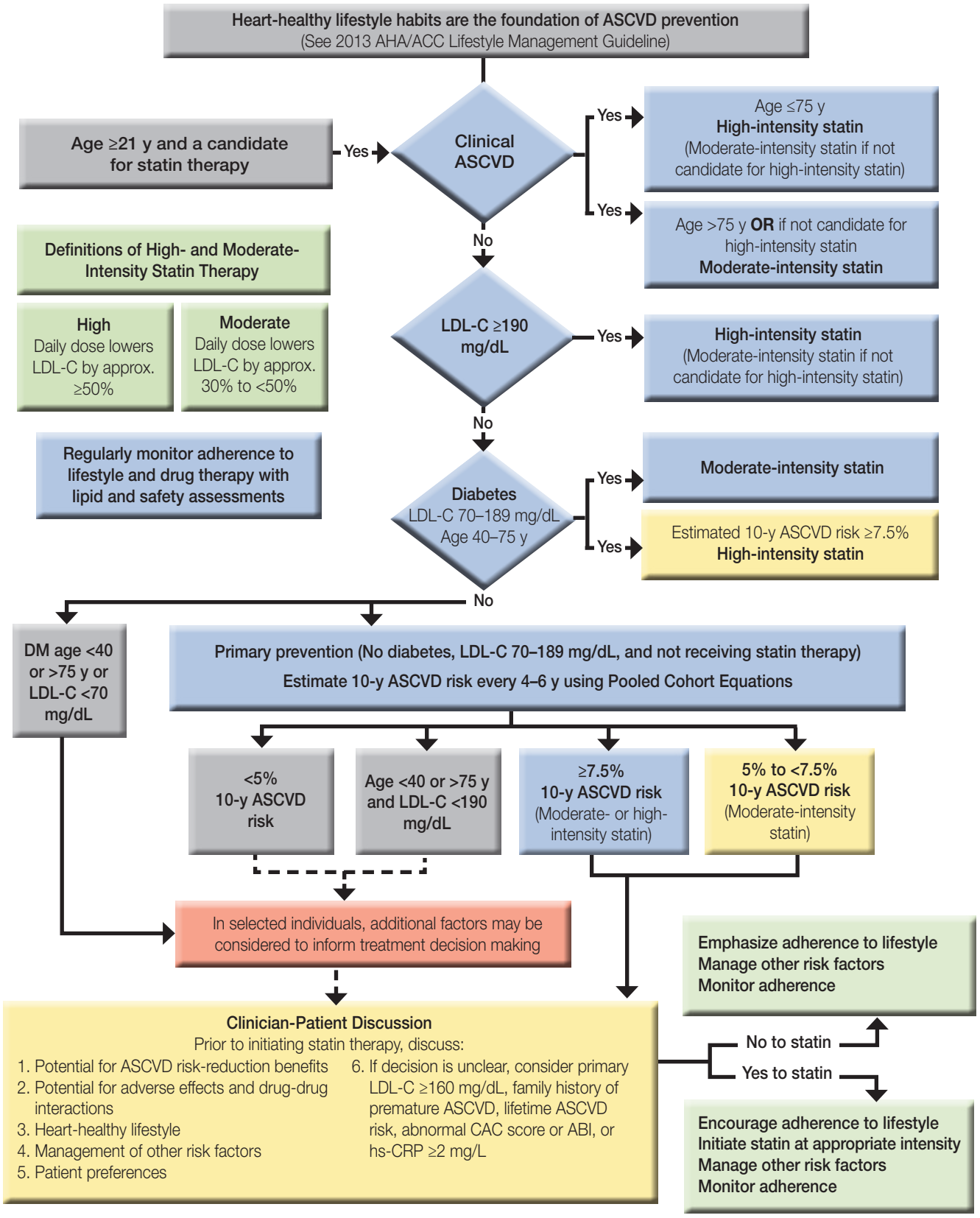
Matthew Mitchell, PharmD

A new category of biologic agents for treatment of hypercholesterolemia, known as PCSK9 inhibitors, is being introduced to the U.S. market. Named for their mechanism of action, the PCSK9 inhibitors are in various stages of FDA review and clinical development. Significantly, the evaluation of this new therapeutic class is occurring simultaneously with a transition in the approach to the treatment of hypercholesterolemia. In 2013 the American College of Cardiology (ACC) and the American Heart Association (AHA) released the revised *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*. These recommendations are summarized in Figure 1. The most noteworthy change was the elimination of the former, clearly defined specific LDL-C numeric treatment goals recognized as the objective of treatment of hypercholesterolemia. In the absence of specific target levels, the revised guidelines focus on cardiovascular risk reduction in high-risk patient populations by managing hypercholesterolemia through the effective use of HMG CoA reductase inhibitors, or "statins." In response to these changes, the Centers for Medicare & Medicaid Services (CMS) and the National Committee for Quality Assurance (NCQA) announced changes to HEDIS®† and Star measures for the coming year; the 2015 American Diabetes Association Guidelines for management of cholesterol in diabetics have been updated; and national evidence-based practice guidelines, which serve as the cornerstone for health plan policy for treatment of hypercholesterolemia, are being restructured. The revised policies will have implications for health care system uptake and utilization of new, "non-statin" therapies for the management of hypercholesterolemia, particularly the PCSK9 inhibitors.

## Disease Treatment and Overview

As described, the 2013 revisions to the ACC/AHA guidelines remove specific LDL-C target goals. The stated rationale for this change is that no studies have focused on treatment or titration to a specific LDL-C goal in adults with clinical atherosclerotic cardiovascular disease (ASCVD). The majority of randomized controlled studies that demonstrated the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed dose of a statin to lower LDL-C levels.[1] The new, revised guidelines recommend lipid screening for primary prevention at five-year intervals, and lifestyle modifications as a first step for all patients. The central focus of statin-based pharmacotherapy is the reduction of risk of ASCVD through the use of

## Figure 1: Summary of Statin Initiation Recommendations to Reduce ASCVD Risk[4]



moderate- or high-intensity statin therapy. Guidelines recommend a reduction of LDL-C by 50 percent in high-risk patients through the use of intensive statin therapy. Patients ≥75 years of age or not a candidate for high-intensity statins are advised to work toward a decrease in LDL-C of 30 to 50 percent by using moderate-intensity statins. As stated previously, the guidelines do not identify specific cholesterol goals and do not address use of non-statin therapies. In response to the revised guidelines, the NCQA announced plans to retire the HEDIS measure *Cholesterol Management for Patients with Cardiovascular Conditions* for 2015. This keeps HEDIS measures aligned with the removal of treatment targets for LDL-C for primary or secondary prevention of ASCVD. The NCQA clearly defines the objective of the change as being to remain consistent with the ACC/AHA guidelines focusing on statin therapy for patients with ASCVD and not on LDL-C control or on LDL-C screening.[1]

Likewise, the HEDIS Comprehensive Diabetes Care Guideline is being modified to eliminate the LDL-C screening and LDL-C control (<100 mg/dL) goals,[2] and the American Diabetes Association (ADA) guideline revisions for 2015 include removal of target LDL-C goals in the diabetic population. Rather, the lipid monitoring guidance consists of a screening lipid profile at diabetes diagnosis, at an initial medical evaluation and/or at 40 years of age, and periodically thereafter.[3]

The revised guidelines recommend moderate- or high-intensity statin therapy for the following four groups:

- Secondary Prevention — Individuals with clinical ASCVD;
- Primary Prevention — Individuals with an LDL-C of 190 mg/dL or higher;
- Primary Prevention — Individuals with type 2 diabetes, between 40 and 75 years of age; and
- Primary Prevention — Individuals with an estimated 10-year risk of cardiovascular disease of 7.5 percent or higher (based on Pooled Cohort Risk Assessment Equations, included in the revised guidelines), who are between 40 and 75 years of age

These guideline changes are expected to influence management of hypercholesterolemia by impacting recommendations for appropriate utilization and health plan–approved indications for use of PCSK9 inhibitors.

## PCSK9 Proteins and PCSK9 Inhibitors — Description and Mechanism of Action

PCSK9 is the recognized name for proprotein convertase subtilisin/kexin type 9. The PCSK9 gene directs the manufacture of PCSK9 protein (primarily in the liver and intestines) that regulates the amount of cholesterol in the bloodstream. In some individuals, due to a PCSK9 gene mutation, there is a change in a single amino acid, which enhances the activity of the PCSK9 protein. The PCSK9 protein controls the number of low-density lipoprotein (LDL) receptors on the surface of cells, most of which are in the liver. These receptors bind low-density lipoproteins, the primary carriers of cholesterol in the blood. The number of LDL receptors on the surface of liver cells determines the rate at which the body can clear cholesterol from the bloodstream. When levels of PCSK9 are elevated, the protein binds the LDL receptors, resulting in fewer available receptors due to their breakdown and decreased re-emergence.[5] Fewer receptors causes decreased receptor-mediated catabolism of LDL-C, leading to high plasma LDL-C levels and contributing to hypercholesterolemia.[6] Therefore, in genetically predisposed individuals, an excess in PCSK9 protein may lead to an accumulation of cholesterol and potentially to a corresponding increase in risk of ASCVD.[7] Individuals with hypercholesterolemia associ-

**Table 1 Familial Hypercholesterolemia Phenotypes and Their Genetic Causes[8]**

| | Heterozygous | Homozygous |
|---|---|---|
| Clinical features | Tendon xanthoma<br><br>Coronary disease >25 years<br>5 mmol/L < LDLC < 12 mmol/L | Tendon xanthoma<br>Cutaneous xanthoma<br>Coronary disease <25 years<br>LDLC > 12 mmol/L<br>(Less in phytosterolaemia and CTX) |
| Genetic disorders | LDL receptor: 1 allele<br>apoB: 1 or 2 alleles<br>NARC1: 1 allele | LDL receptor both alleles<br>no gene dose effect<br>not yet described<br>ARH<br>Phytosterolaemia<br>CTX |

**Table 2 Diagnostic Criteria for Diagnosis of Heterozygous Familial Hypercholesterolemia[10]**

| | Criteria | Score |
|---|---|---|
| Family history | First-degree adult relative with:<br>• Premature coronary and/or vascular disease (male <55 years; female <60 years)<br>• LDL-C >95th percentile for age and gender<br>• Tendon xanthomata and/or arcus cornealis | 1 |
| | First-degree relative <18 years with LDL-C >95th percentile for age and gender | 2 |
| Clinical history | Patient has premature ischemic heart disease (IHD) (ages as above) | 2 |
| | Patient has premature vascular and/or cerebrovascular disease (ages as above) | 1 |
| Physical examination | Tendon xanthomata | 6 |
| | Arcus cornealis prior to age 45 | 4 |
| LDL-C | >8.5 mmol/L (more than 330 mg/dL) | 8 |
| | 6.5–8.4 mmol/L (250–329 mg/dL) | 5 |
| | 5.0–6.4 mmol/L (190–249 mg/dL) | 3 |
| | 4.0–4.9 mmol/L (155–189 mg/dL) | 1 |
| Definite FH | - | Score >8 |
| Probable FH | - | Score 6–8 |
| Possible FH | - | Score 3–5 |
| No diagnosis | - | Score <3 |

**Table 3 PCSK9 Inhibitors Submitted or Pending FDA Submission**

| Drug Name | Manufacturer | Medication Class | FDA Submission Status |
|---|---|---|---|
| Alirocumab | Regeneron/Sanofi | PCSK9 inhibitor | Submitted in January 2015; with review by July 24, 2015 |
| Evolocumab | Amgen | PCSK9 inhibitor | Submitted to FDA; PDUFA scheduled for August 27, 2015 |
| Bococizumab | Pfizer | PCSK9 inhibitor | Planned submission in 2016 |

**Table 4 Populations in Which PCSK9 Inhibitors Have Demonstrated Efficacy (Based Upon Currently Published Clinical Studies)**

| Treatment Population | Alirocumab | Evolocumab |
|---|---|---|
| Hereditary familial hypercholesterolemia (heterozygous) | √ | √ |
| Hereditary familial hypercholesterolemia (homozygous) | N/A | √ |
| Statin intolerance | √ | √ |
| Primary treatment as monotherapy (without statins) | √ | √ |
| Patients with LDL-C above treatment goal despite maximal background lipid therapy | √ | √ |
| Secondary prevention | √ | √ |

**Table 5 Dosing and Administration**

| Drug name | Adult Dose |
|---|---|
| Alirocumab | Initial 75 mg SC every two weeks; maintenance 75 mg to 150 mg SC every two weeks* |
| Evolocumab | 140 mg SC every two weeks or 420 mg SC every four weeks |

*Monthly dosing for alirocumab may also be available based on the results from the CHOICE studies

ated with an LDL receptor defect are identified as having familial hypercholesterolemia, which has been loosely categorized as either heterozygous or homozygous. Table 1 indicates the clinical and genetic aspects of these variants of hypercholesterolemia.

The worldwide prevalence of heterozygous familial hypercholesterolemia has long been estimated as one in 500 individuals. Prevalence of the homozygous hypercholesterolemia variant has historically been estimated as one in 1 million individuals. Recent World Health Organization reports suggest the incidence could be higher.[9] Criteria for the diagnosis of familial hypercholesterolemia are identified in Table 2.

## Overview of PCSK9 Inhibitor Class

The PCSK9 inhibitors currently being studied or awaiting FDA approval are human monoclonal antibodies that inhibit the PCSK9 protein. Left unchecked, the protein targets LDL receptors, resulting in degradation of receptors, effectively reducing the efficiency of the liver in removing LDL-C from the blood.[9] The PCSK9 inhibitors are designed to bind to PCSK9 and inhibit it from binding to LDL receptors on the liver surface. The result is the reduction in the amount of PCSK9 protein, effectively allowing more LDL receptors to populate the surface of the liver, capable of removing LDL-C from the bloodstream.[11] In most cases, the use of PCSK9 inhibitors will be in conjunction with high-intensity statin therapy, unless patients are not a candidate for statins.

## Clinical Studies

Alirocumab (Sanofi and Regeneron) was studied for its ability to achieve an LDL-C reduction to less than 100 mg/dL and 70 mg/dL in a 12-week modified intent-to-treat population, compared with placebo (see Figure 2).

Subsequently undertaken phase 3 clinical trials for alirocumab include nine trials conducted under the umbrella of "ODYSSEY trials," to assess attainment of primary efficacy endpoints in patients at 24 weeks compared to placebo or to an active comparator. Patients were treated with alirocumab in addition to standard-of-care lipid-lowering therapy, except for those enrolled in the ODYSSEY ALTERNATIVE study. The ODYSSEY LONG TERM trial was undertaken to assess long-term safety and efficacy in 2,341 individuals with hypercholesterolemia of more than 70 mg/dL at baseline. Patients were treated with alirocumab at a dose of 150 mg every two weeks. Cardiovascular risk for this group was assessed as being high or very high with maximally tolerated statins. Of these subjects, 18 percent were identified as having heterozygous familial hypercholesterolemia (HeFH). Primary efficacy endpoint for this study was at 24 weeks, with a safety analysis performed at one year; 25 percent of patients reached 18 months of treatment. Patients with HeFH demonstrated an LDL-C reduction of 56.3 percent (vs. a decrease of 7 percent in the placebo group). The reduction at week 24 of LDL-C was 62.1 percent in the non-HeFH population, compared to a 0.5 percent decrease in the placebo group. Additionally, post hoc cardiovascular outcomes pooled data from the ODYSSEY LONG TERM, HIGH FH, COMBO I, FH1, and FH2 studies indicate a lower rate of adjudicated major cardiovascular events (cardiac death, myocardial infarction, stroke, and unstable angina requiring hospitalization) compared to placebo (p-value <0.05). The ODYSSEY OUTCOMES trial is under way to support the prospective assessment of cardiovascular outcomes. Data from the ODYSSEY CHOICE I and CHOICE II studies demonstrate attainment of cholesterol-lowering endpoints in patients treated with monthly doses of alirocumab versus placebo in patients with hypercholesterolemia. ODYSSEY CHOICE I assessed the efficacy and

**Figure 2: Impact of Alirocumab on LDL-C Levels**

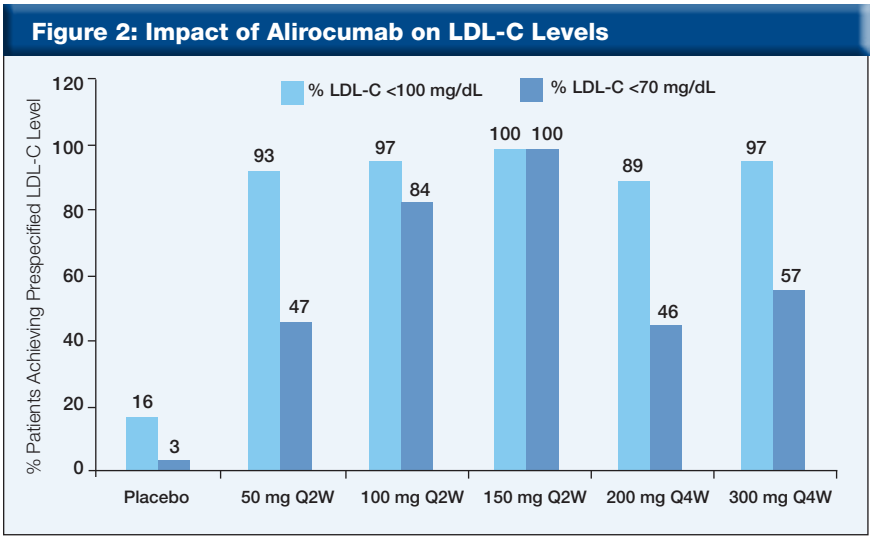
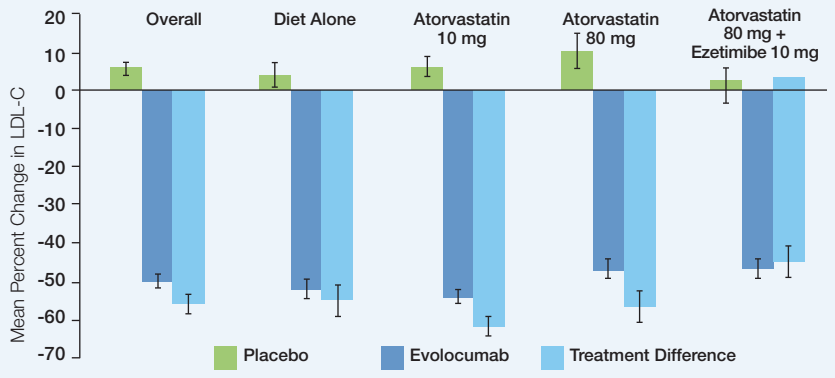


**Figure 3: Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES Study) — Evolocumab**




Error bars represent standard error for treatment difference
Treatment difference is least squares mean derived from a repeated measures model

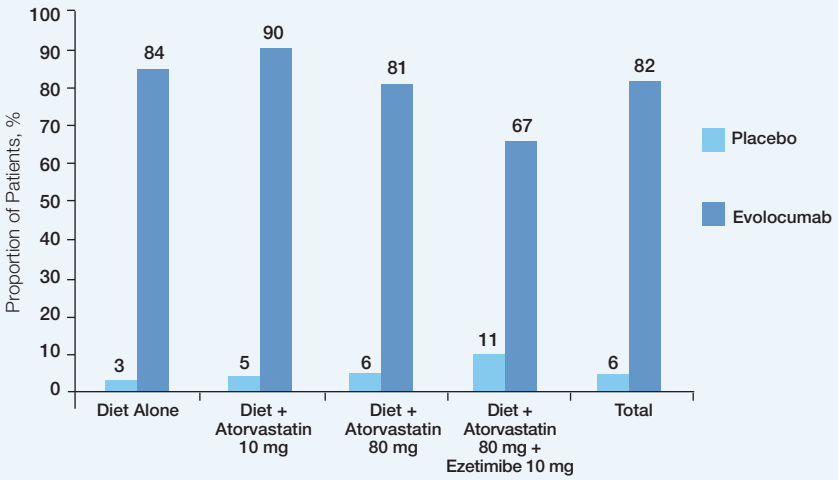
safety of alirocumab in patients with hypercholesterolemia at moderate-to-high cardiovascular (CV) risk, and ODYSSEY CHOICE II evaluated the drug in patients with hypercholesterolemia with high CV risk and/or a history of intolerance to two or more statins. Both the studies met the primary endpoint.

Likewise, evolocumab (Amgen) includes the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES Study). In this 52-week study of 905 patients, patients consisted of four background therapy groups including diet alone, atorvastatin 10 mg, atorvastatin 80 mg, or atorvastatin 80 mg plus ezetimibe (See Figure 3).

Attainment of LDL-C goal of <70 mg/dL at week 52 was demonstrated in the DESCARTES Study as shown in Figure 4.

DESCARTES results for the 52-week study demonstrated that, when treated with 420 mg of evolocumab monthly, patients with a wide range of cardiovascular risk profiles and with background lipid-lowering therapy exhibited an adjusted LDL-C reduction of 51.5 percent, compared with an increase of 6.0 percent in the placebo group. The treatment difference was consistent for all background therapy groups.

**Figure 4: DESCARTES Study — Patients Attaining LDL-C of <70 mg/dL at 52 Weeks with Evolocumab**




The cardiovascular outcome trial for evolocumab is ongoing as well.

Both evolocumab and alirocumab demonstrated similar adverse event profiles compared with placebo. The most common adverse events in alirocumab-treated patients were back pain, nasopharyngitis, upper respiratory tract infection, and hypertension (frequency does not appear to differ from placebo groups).

The most common adverse events in evolocumab-treated patients were back pain, arthralgia, headache, muscle spasms, and pain in extremity (all <2 percent). Both alirocumab and evolocumab are well tolerated and, based upon available clinical trials, have comparable safety profiles.

## Status of Submission to FDA

Amgen's PCSK9 inhibitor, evolocumab, has been submitted for FDA review, with an anticipated Prescription Drug User Fee Act (PDUFA) target action date of August 27, 2015 (See Table 3). Sanofi/Regeneron submitted their product, alirocumab, to the FDA in January 2015, with a scheduled review by July 24, 2015, and Pfizer has announced plans to file for FDA approval of bococizumab

in 2016. Currently available and published studies demonstrate the efficacy of the PCSK9 inhibitors relative to placebo and to statins. Although not presently available, outcomes studies demonstrating the effect of these therapies on cardiovascular outcomes are awaited, and it is reported that all three PCSK9 phase 3 programs will include a cardiovascular outcomes trial (CVOT).

## Potential FDA Labeling Scenarios

The anticipated FDA approval scenarios for these drugs will likely include treatment as adjunct to diet and lifestyle modification. Indications for treatment of individuals with heterozygous familial hypercholesterolemia will likely be included for alirocumab. Evolocumab may be indicated for both hereditary heterozygous and homozygous familial hypercholesterolemia. Further details regarding relevant history of cardiovascular disease, concomitant therapy with statins (except in patients who are not candidates for statin therapy), 10-year risk of ASCVD†† and other disease variants await definition within the FDA-approved labeling.

## Uptake and Use

The PCSK9 inhibitors offer clinicians and patients a highly effective treatment for resistant hypercholesterolemia. The hereditary familial hypercholesterolemia patient population may be the initial target population in agreement with providers and payors. Identifying appropriate administrative criteria will be a significant factor for plans in managing the extensive patient population who are potential candidates for use of the PCSK9 inhibitors. Enthusiasm for the role these agents may play in improving health outcomes will play against the backdrop of revised guidelines for treatment of hypercholesterolemia, in patients for whom this is the primary diagnosis as well as those with diabetes. Efforts to demonstrate that patients are adherent to high-intensity statin therapy prior to allowing access to these new biologic therapies may be important for payors trying to manage this new pharmacologic class. Also key is a better consensus of defining statin intolerance. Although these products have demonstrated profound reductions in LDL-C, payors will have to juggle the clinical benefits with the financial challenges. However, for the longer term, if the PCSK9 inhibitors are able to demonstrate substantial reduction in long-term cardiovascular outcomes, then these products will likely represent a major breakthrough in the management of cardiovascular disease.

† HEDIS is a registered trademark of the National Committee for Quality Assurance.

††The guideline recommends using the new Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke) for the identification of candidates for statin therapy. The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at **http://my.americanheart.org/cvriskcalculator** and **www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx**.

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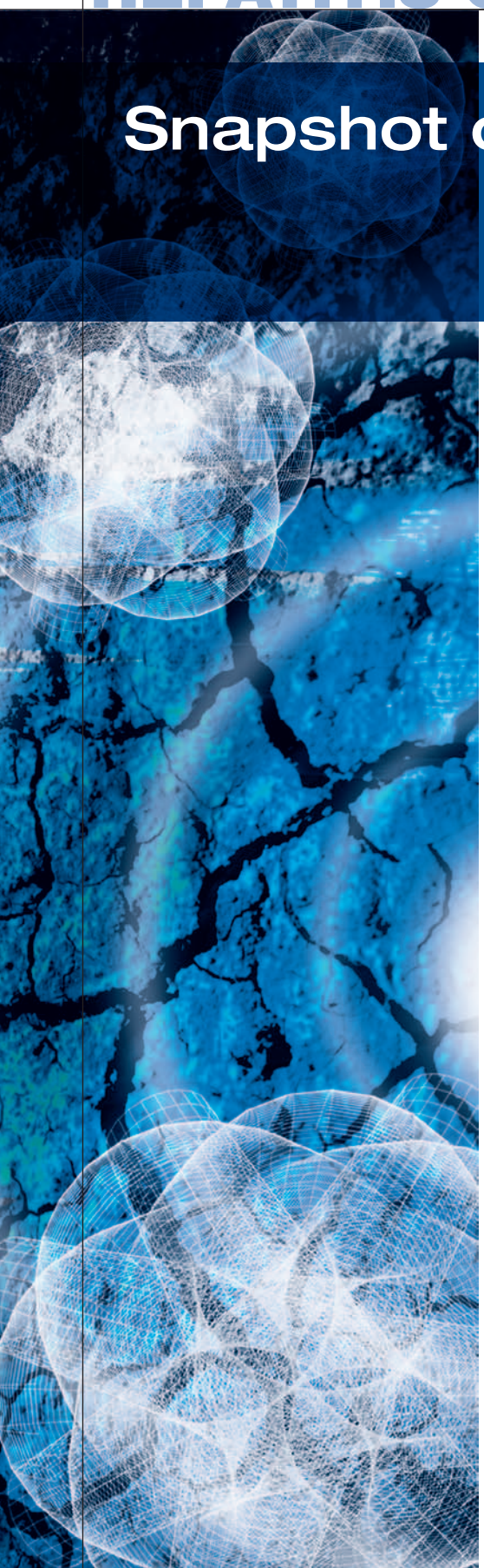


# Snapshot of the HCV Landscape:
## Moving Forward from 2014

*Maria Lopes, MD, MS, Chief Medical Officer, Magellan Rx Management; and*
*Jim Rebello, PharmD, Sr. Director, Account Management, Magellan Rx Management*

Maria Lopes, MD, MS

Jim Rebello, PharmD

Treatment strategies for hepatitis C virus (HCV) therapy have undergone a rapid evolution since December 2013. The approval of the nucleotide polymerase inhibitor sofosbuvir was a major breakthrough for HCV patients, allowing for potential all-oral interferon regimens. Sofosbuvir quickly took over the HCV market, obtaining the coveted award of "the fastest drug launch ever," posting a record-breaking $5.7 billion in sales in the first half of 2014.[1] The number of HCV patients awaiting therapy (~3,000,000) and the price of the regimen ($84,000 for 12 weeks) have been driving the growth.[2] In the first half of 2014, sofosbuvir cured approximately 9,000 patients.

The indication for sofosbuvir in the United States is multifaceted. Sovaldi® (sofosbuvir 400 mg tablets) is indicated for genotype 1 or 4 with peginterferon and ribavirin for 12 weeks; in genotype 2 with ribavirin alone for 12 weeks; and genotype 3 with ribavirin for 24 weeks.[3] Harvoni®, which is a combination of sofosbuvir 400 mg with ledipasvir, a 90 mg NS5A inhibitor in one tablet, was approved in October 2014.[4] Harvoni can be used for eight weeks (this duration can be considered in treatment naïve patients without cirrhosis who have pretreatment RNA ≤6 million IU/mL), for 12 weeks (in treatment naïve patients with or without cirrhosis and treatment experienced individuals without cirrhosis), and for 24 weeks in treatment experienced patients with cirrhosis. The Harvoni WAC price is listed as $94,500 for a 12-week regimen.[2]

Adding to the paradigm, in December 2014 the FDA approved AbbVie's Viekira Pak™, a combination pack containing ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir (CYP3A inhibitor), and dasabuvir (non-nucleoside NS5B polymerase inhibitor).[5] Interestingly, the approval contained variations in regimen length between patients with genotype 1a vs. 1b. Dosing guidelines indicate patients with genotype 1a without cirrhosis and genotype 1b, with or without cirrhosis, should be treated for 12 weeks. However, patients with HCV genotype 1a *with* cirrhosis are advised to take the Viekira regimen for 12 to 24 weeks, based on prior treatment his-

**Table 1 Oral Regimens for Chronic Hepatitis C (Phase 3 Trials)[3–5]**

| Population | Regimen | Clinical Trial SVR | Duration | Cost |
|---|---|---|---|---|
| Genotype 1 Naïve | Harvoni ± RBV | 92–100% | 8–12 weeks* | $63,000–$94,500 |
| | Viekira ± RBV | 90–100% | 12 weeks | $83,319 |
| Genotype 1 Treatment Experienced W/O Cirrhosis | Harvoni ± RBV | 87–100% | 12 weeks | $94,500 |
| | Viekira ± RBV | 93–100% | 12 weeks | $83,319 |
| Genotype 1 Treatment Experienced WITH Cirrhosis | Harvoni ± RBV | 100% | 24 weeks | $189,000 |
| | Viekira ± RBV | GT 1b: 98%<br>GT 1a: 95% | 12 weeks (GT 1b)<br>24 weeks (GT 1a)† | $83,319–$166,638 |
| Genotype 2 | Sovaldi + RBV | 93–95% | 12 weeks | $84,000 |
| Genotype 3 Naïve | Sovaldi + RBV | 93–94% | 24 weeks | $168,000 |
| Genotype 3 Experienced | Sovaldi + RBV | 77–79% | 24 weeks | $168,000 |

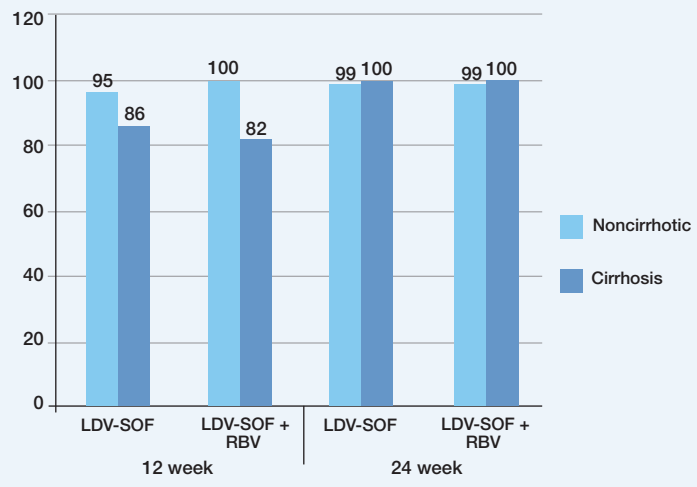
*Considerations for eight-week dosing with Harvoni can be made in treatment naïve, noncirrhotic patients with pretreatment HCV RNA <6MM IU/mL
†May be appropriate for 12 weeks of therapy based on response to prior treatment

tory. Current reports price the regimen at $83,319 for 12 weeks.[2]

Harvoni and Viekira fill a significant void for genotype 1 HCV patients, especially those without cirrhosis. Treatment of genotype 3 patients, treatment experienced cirrhotics, and decompensated cirrhotic patients remains an unmet need. For HCV patients, customized treatment approaches are crucial.

From a clinical trial perspective, we can break down a specific genotype HCV patient into: treatment naïve without cirrhosis, with cirrhosis, treatment experienced with cirrhosis, and without cirrhosis. Table 1 shows a version of this breakdown that is simplified based on the variations included in the Harvoni and Viekira package inserts.

**Figure 1: Ion-2: SVR Results[4]**




## Clinical Trials

Harvoni's package insert defines three clinical trials (Ion-1, Ion-2, and Ion-3). Ion-3 established the efficacy of Harvoni in noncirrhotic treatment naïve patients with genotype 1 HCV.

In this treatment naïve, noncirrhotic population, Harvoni (without RBV) saw SVR rates of 94 percent and 96 percent for patients with treatment of eight weeks and 12 weeks duration, respectively. However, the eight-week regimen saw an increase in patient relapse when patients had a baseline HCV RNA ≥6 million IU/mL, which led to the requirement of 12-week duration of therapy for patients with this baseline status of HCV RNA.

Ion-1's study population included genotype 1, treatment naïve patients with and without cirrhosis, treated for 12 and 24 weeks with and without ribavirin. Harvoni showed similar efficacy across all patient populations varying from 97 to 100 percent. Lastly, Ion-2 was Gilead's study of treatment experienced genotype 1 patients with

**Table 2 Select Viekira Phase 3 Clinical Trials[5]**

| Clinical Trial | Regimen | Population | SVR 12 | Comments |
|---|---|---|---|---|
| Sapphire - 1 | Viekira + RBV x 12 weeks | GT 1a + 1b treatment naïve without cirrhosis | Overall SVR: 96% | Similar SVR across both 1a and 1b |
| Pearl 3 + Pearl 4 | Viekira ± RBV x 12 weeks | GT 1b and GT 1a treatment naïve without cirrhosis | GT 1b:<br>Viekira: 100%<br>Viekira + RBV: 99% | Pearl 3 included GT 1b patients |
| | | | GT 1a:<br>Viekira: 90%<br>Viekira + RBV: 97% | Pearl 4 included GT 1a patients |
| Sapphire - 2 | Viekira + RBV x 12 weeks | GT 1a and GT 1b treatment experienced without cirrhosis | Overall SVR: 96% | |
| Pearl - 2 | Viekira ± RBV x 12 weeks | GT 1b treatment experienced without cirrhosis | Viekira: 100%<br>Viekira + RBV: 97% | |
| Turquoise - 2 | Viekira + RBV x 12/24 weeks | GT 1a and GT 1b treatment naïve and experienced with cirrhosis | GT 1a:<br>Viekira + RBV X 12 weeks: 89%<br>Viekira + RBV X 24 weeks: 94% | Rates for GT 1a decrease in prior null responders with the 12-week regimen |
| | | | GT 1b:<br>Viekira + RBV X 12 weeks: 99%<br>Viekira + RBV X 24 weeks: 100% | |

and without cirrhosis. Harvoni was administered with and without ribavirin for 12 and 24 weeks. When broken out by patients with and without cirrhosis, the study showed the results seen in Figure 1.

The difference between the 12- and 24-week duration in treatment experienced cirrhotics (86 percent vs. 100 percent, respectively) resulted in a change in dosing guidelines and recommendations for a 24-week dosing regimen costing $189,000. The Harvoni label only includes regimens for genotype 1 patients. Thus, the only all-oral regimen for patients with genotype 3 is Sovaldi in combination with ribavirin for 24 weeks, a $168,000 regimen that results in overall SVR of 84 percent. However, in phase 3 trials of treatment experienced cirrhotics, response in this group fell to 60 percent.

The Viekira package insert consists of the six phase 3 clinical trials shown in Table 2.[5] The package insert includes findings from phase 3 trials across genotype 1a, 1b, naïve, experienced, and cirrhotic patients. The Turquoise - 2 trial saw a difference in SVR rates for 12- vs. 24-week regimens for treatment experienced patients with genotype 1a with cirrhosis. Outside of this population, the recom-

The analysis of claims-based data is significant; it corroborates clinical trial data, and it demonstrates that SVR rates can drop in less controlled environments. These findings underscore the importance of health plan monitoring of HCV therapies and giving consideration to the unique attributes of each plan's population.

mended treatment duration for other patient populations is 12 weeks of therapy. Although the proportion of patients expected to require 24 weeks of Viekira therapy is small, treatment of this subset will cost $166,000 per patient.

## Real-World Results

The initial findings from real-world data cohorts are fairly corroborative of clinical trial data. The first issued report came from CVS Pharmacy, where discontinuation rates were analyzed based on claims data.

The overall discontinuation rate appeared to be 8.1 percent, which is surprisingly low for a claims-based analysis.[6] Additionally, real-world data was presented at the most recent American Association for the Study of Liver Diseases (AASLD) conference. Data was presented from two real-world analyses.

The first was HCV-Target, a large (>2,000 patients) HCV registry consisting mainly of academic centers. HCV-Target saw SVR4 rates (which have a ≥94 percent concordance with SVR12) of 89 percent for genotype 1 patients treated with sofosbuvir and simeprevir.[7] The second analysis came from the TRIO health database, which utilizes data from specialty pharmacies.[8] This analysis saw an average SVR12 rate of 79 percent in an ITT population for genotype 1 simeprevir and sofosbuvir patients. Though, in genotype 1 naïve noncirrhotics the SVR12 rate was closer to 88 percent.

The analysis of claims-based data is significant; it corroborates clinical trial data, and it demonstrates that SVR rates can drop in less controlled environments. These findings underscore the importance of health plan monitoring of HCV therapies and giving consideration to the unique attributes of each plan's population.

If a patient population contains a significantly higher percentage of patients with cirrhosis or genotype 3, this population will be significantly more difficult (and costly) to treat. This issue becomes more complex when analyzing adherence. Rates of adherence to HCV regimens will be falsely elevated due to the short treatment duration. An approach that utilizes patient-reported adherence in addition to claims data may provide a more global picture.

## Cross-Trial Comparisons

So, how should one compare the AbbVie and Gilead regimens? This is a complex question. It is important to recognize that cross-trial comparisons for HCV are not necessarily appropriate because of potential differences in baseline characteristics. Indirect comparisons may help adjust for baseline differences. Though, in general, for the HCV genotype 1 population, it is highly likely that these two regimens are not statistically significantly different related to sustained viral response and that physicians have a generally positive view of utilizing both regimens.

Additionally, both regimens are recommended in the latest update of the AASLD guidelines. Unfortunately, accurately assessing the proportion of patients for whom short (eight weeks) versus long (24 weeks) durations of therapy are appropriate is difficult. Answering this question can help to identify the most cost-effective product for the management of HCV, especially in genotype 1 patients. Although it is projected the majority of patients will fall within the 12-week treatment for both Harvoni and Viekira, utilization of these products in the first several months of 2015 will help to address this question.

Harvoni and Viekira will be the main players for the treatment of genotype 1 patients in 2015. Potential regimens to fulfill the need for genotype 3 patients may reach the market in early 2016 with either BMS' daclatasvir and Sovaldi combo regimen or Gilead's own GS-5816 and Sovaldi combo. In the interim, the current regimens are suitable for treatment of most genotype 1 patients with chronic HCV.

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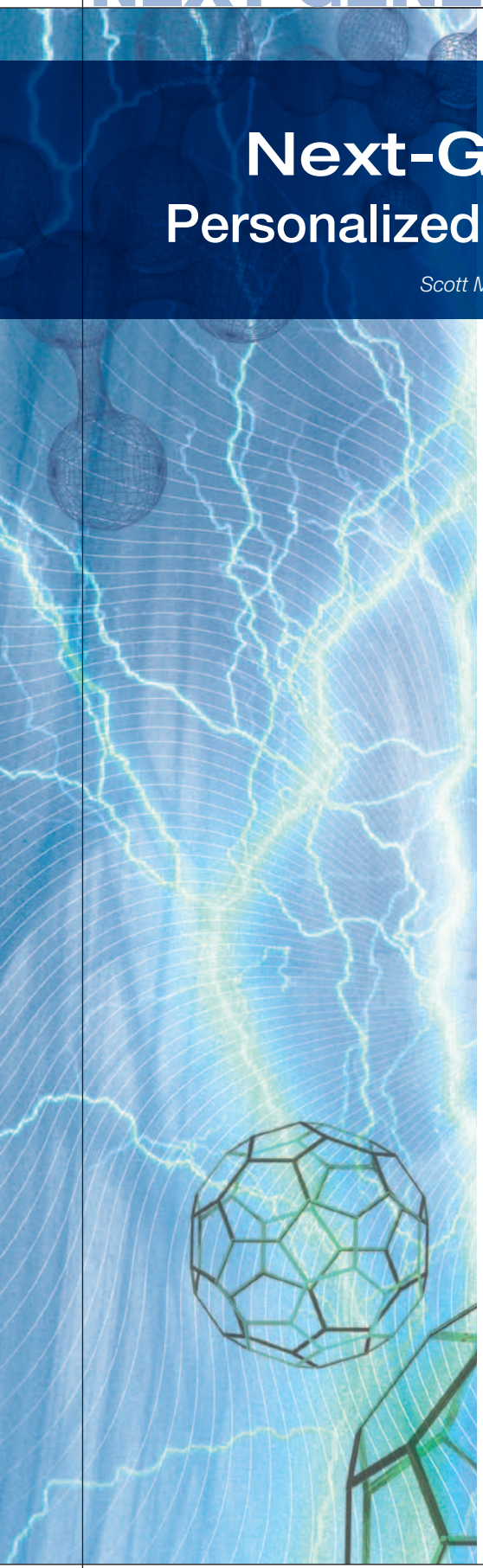

# Next-Generation Sequencing: Personalized Medicine for Oncology Patients

*Scott McClelland, PharmD, Senior Director of Pharmacy, Florida Blue; and Janet McIntyre, MA*

## Introduction

Scott McClelland, PharmD

Janet McIntyre, MA

The increasing use of next-generation sequencing (NGS) is radically changing oncology both in the approach to diagnoses and treatments. Today, NGS panels can identify mutations associated with hereditary cancer syndromes, such as BRCA1/BRCA2 and Lynch syndrome, and guide the use of targeted therapeutic agents specifically designed to combat the unique characteristics of individual cancer subtypes. NGS or second-generation sequencing is a generic term referring to DNA sequencing methods used for massive parallel sequencing of small regions (exomes) or an entire genome. NGS technology enables identification of cancer-related genetic mutations. Offered across a variety of platforms since 2008, NGS provides a faster and higher throughput option compared to traditional techniques. Entire genomes can be mapped out in a week's time, and targeted sequencing assays to assess genes associated with colon, ovarian, prostate, and thyroid cancers can be performed in a day.

NGS also represents a breakthrough in accessibility. Costs to sequence one genome have decreased from approximately $95,000 using Sanger sequencing in 2001 to just under $5,000 in mid-2014 with the use of NGS.[1] Lowered costs make the sophisticated genomic testing and analysis more widely available and less expensive than, for example, conducting three separate oncogene tests — anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), and KRAS — for non-small cell lung cancer.

## Oncology and Personalized Medicine

NGS is providing a road map of cancer that represents a departure from past cancer diagnoses classified by anatomic origin, microscopic morphology, or immunohistology.[2-5] By analyzing predictive biomarkers or the genetic makeup of cancerous cells obtained through NGS, clinicians can more accurately assess patient-specific risks, make diagnoses, and develop targeted interventions. Additionally, NGS can be used to risk-stratify cancer patients for the purposes of avoiding chemotherapy in cases where it may not add benefit. This "personalized medicine" approach consists of the diagnostic test and the therapeutic intervention targeted for an individual based on his or her genetics.[6]

NGS permits a systematic approach to health care that takes advantage of not only DNA data, but also information related to RNA, proteins, metabolites,

networks, cells, and tissues.[7,8] Molecular and cellular data allow researchers and clinicians to stratify cancers in a way that was not possible previously through pathology.[7] Oncology is one of the fastest-growing areas for disease definition on a molecular basis, with previously thought homogeneous cancers now being subcategorized and stratified through the use of NGS.

## Aetna Health Plans and Personalized Medicine

In 1998 Aetna created a program for BRCA mutations in inherited breast and ovarian cancer, becoming one of the first health plans to develop a policy for the use of genetic information and personalized genetic medicine. Today, Aetna maintains a Clinical Policy Unit that is tasked with reviewing relevant medical literature to establish both the clinical validity and clinical utility of new technologies by evaluating the following criteria:

- The technology must have final approval from the appropriate governmental regulatory bodies, when required.
- The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
- The technology must improve net health outcome.
- The technology must be as beneficial as any established alternatives.
- The improvement must be attainable outside investigational settings.

Guidance for new technologies are classified as Clinical Policy Bulletins (CPBs) and are reviewed annually. The bulletins identify benefits of the new technology and criteria for the populations it would benefit. Aetna CPBs for genetic testing require that the following criteria must be met for a test to be considered medically necessary for disease diagnosis:

- The patient displays clinical features, or is at direct risk of inheriting the mutation in question (presymptomatic); and
- The result of the test will directly impact the treatment; and
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, and one disease diagnosis, as defined by Aetna, is suspected.

An example of genetic screening not meeting these criteria would be the ApoE genetic test, which has been proven to predict cases of early-onset Alzheimer's disease. However, there is no proven treatment to prevent the disease from developing, so while the test is effective, it has no impact on patient treatment. Once a CPB draft has received all necessary internal approvals, the clinical policy team implements the policy within the Aetna system.

While genetic testing currently accounts for less than 1 percent of their total medical spending, Aetna recognizes the growth potential and has instituted programs to guide utilization of genetic testing. An example of this was the Active Health CareEngine analytics tool, part of a system that integrates claims data with demographic information to identify trends in personal and family history that serve as indicators for genetic mutations relating to breast and ovarian cancer. The system identifies plan members appropriate for genetic screening, prompting them to speak to their physician or a genetic counselor. A network of telephone-based multidisciplinary clinical care managers is available to help patients explore their options.

Aetna applies genetic testing in the diagnostic testing space, with the utilization of genetic information as a prerequisite for plan coverage of specific high-cost therapies. An example of this would be approval for the use of Erbitux® or Vectibix® for colorectal cancer. Evidence of KRAS mutation genetic testing is required prior to drug approval in order to ensure the patient is receiving the correct (and most cost-effective) treatment for their disease.

## Florida Blue Applies NGS

At Florida Blue, the value and applicability of progress made in NGS and personalized medicine is evident in the integration of genetic testing within the medical and pharmacy policies. Among the medical policies, guidelines define coverage parameters for genetic testing, indicating in which situations scientific evidence supports the use of genetic testing. Genetic testing requirements may be included in medical policies defining the need for genetic tests to establish the diagnosis of certain inheritable diseases, for certain prenatal diagnostic tests, or for specific genetic testing related to particular disease states and their potential treatments. It is within this latter category that Florida Blue's medical policies address the role of genetic testing for the diagnosis and treatment of diseases and conditions, such as hereditary breast or ovarian cancer, colon cancer, and other conditions. Florida Blue makes available to providers a clear set of criteria for genetic tests, and the criteria identified by the plan as supporting the medical necessity of genetic tests, or the rationale for consideration of the test as experimental or investigational.

Within the prescription drug prior authorization process, multiple oncology drugs are supported with clear guidelines governing their appropriate use. Requisite genetic tests are clearly defined and integrated into the approval guidelines, documents, and review process. The treatment options and opportunities for optimizing patient outcomes through

**Table 1 Genomic Tests and Family History for Oncologic Disorders**

*Tier 1/green category represents genomic and family health history applications which have a base of synthesized evidence supporting implementation into practice.*

| Gene, Gene/Drug, Test, or Family History | Disorder/Indication | Use |
|---|---|---|
| **Cancer — Breast /Ovarian** | | |
| Family history of breast/ovarian or other types of BRCA-related cancer | Hereditary breast and ovarian cancer in women | Risk prediction for referral for BRCA genetic counseling |
| First-degree family history of breast cancer | Chemoprevention of breast cancer | Risk prediction |
| Family history of known breast/ovarian cancer with deleterious BRCA mutation | Hereditary breast and ovarian cancer in women | Risk prediction; referral to counseling for BRCA genetic testing |
| HER2/trastuzumab | Invasive breast cancer | Pharmacogenomics (PGx) |
| HER2/pertuzumab | Invasive breast cancer | PGx |
| HER2/ado-trastuzumab emtansine | Metastatic breast cancer | PGx |
| HER2/everolimus | Advanced HR+ HER2- breast cancer | PGx |
| HER2/lapatinib (in combination with capecitabine or letrozole) | Advanced or metastatic breast cancer | PGx |
| HER2 | Invasive breast cancer | PGx |
| ER/fulvestrant | Metastatic breast cancer | PGx |
| ER/exemestane | ER+ early breast cancer | PGx |
| ER/anastrozole or letrozole | ER+ early invasive breast cancer | PGx |
| ER and PgR | Invasive breast cancer, breast cancer recurrences | PGx |
| Oncotype DX® adjuvant chemotherapy | ER+/LN-/HER2- breast cancer, intermediate risk of recurrence | Prognostic; guiding decision-making: adjuvant chemotherapy |
| **Cancer — Colorectal** | | |
| Testing for Lynch syndrome | Newly diagnosed colorectal cancer | Screening, cascade testing of relatives |
| Testing for Lynch syndrome | Known Lynch syndrome in family | Diagnostic, screening |
| KRAS/cetuximab, panitumumab | Metastatic colorectal cancer | PGx |
| Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5 or CEA) | Invasive colorectal cancer | Prognostic |
| **Cancer — Gastric** | | |
| HER2/trastuzumab | Gastric or gastroesophageal junction adenocarcinoma | PGx |
| c-Kit protein (CD 117)/imatinib | Gastrointestinal stromal tumors | PGx |
| **Cancer — Leukemia/Lymphoma** | | |
| Philadelphia chromosome, T315I mutation/ dasatinib | Chronic myeloid leukemia, acute lymphoblastic leukemia | PGx; diagnostic |
| Philadelphia chromosome/imatinib | Chronic myeloid leukemia, acute lymphoblastic leukemia | PGx; diagnostic |
| Philadelphia chromosome/bosutinib | Chronic myeloid leukemia | PGx; diagnostic |
| Philadelphia chromosome/nilotinib | Chronic myeloid leukemia | PGx; diagnostic |
| PML/RAR$\alpha$/tretinoin | Acute promyelocytic leukemia | PGx |
| PML/RAR$\alpha$/arsenic trioxide | Acute promyelocytic leukemia | PGx |
| PDGFRB/imatinib | Myelodysplastic/myeloproliferative diseases | PGx |
| CD25/denileukin diftitox | Persistent or recurrent cutaneous T-cell lymphoma | PGx |
| CD20/tositumomab | Non-Hodgkin's lymphoma | PGx |
| G6PD/rasburicase | Leukemia, lymphoma, solid tumor malignancies | PGx, pretreatment screening in patients at higher risk for G6PD deficiency (e.g., African or Mediterranean ancestry) |
| Chromosome 5q deletion/lenalidomide | Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q | PGx |

| Gene, Gene/Drug, Test, or Family History | Disorder/Indication | Use |
|---|---|---|
| **Cancer — Lung** | | |
| EGFR (exon 19 deletions and exon 21 (L858R) substitution mutations)/afatinib | Metastatic non-small cell lung cancer | PGx |
| EGFR (exon 19 deletions and exon 21 (L858R) substitution mutations)/erlotinib | Locally advanced or metastatic non-small cell lung cancer | PGx |
| ALK gene rearrangement/crizotinib | Non-small cell lung cancer | PGx |
| **Cancer — Melanoma** | | |
| BRAF V600E/K/trametinib | Unresectable or metastatic melanoma | PGx |
| BRAF V600E/dabrafenib | Unresectable or metastatic melanoma | PGx |
| BRAF V600E/vemurafenib | Unresectable or metastatic melanoma | PGx |

Adapted from Centers for Disease Control and Prevention.[11]

targeted treatments continue to improve as the prior authorization process is growing increasingly sophisticated. This is evident in Florida Blue's integrated and comprehensive oversight process, with requirements including demonstration of the correct diagnosis and evidence of treatment with appropriate alternative or step therapies, as has long been the case. However, the additional requirement that appropriate genetic testing be undertaken is a key consideration in obtaining approval for the use of many oncology agents. For example, Afinitor® criteria require evidence of HER2 testing, Cometriq® approval is incumbent upon testing for RED fusion rearrangement, and Iclusig® prescribers are prompted to provide information regarding the presence of the Philadelphia chromosome. The integration of these diagnostic tests and their significance improves outcomes and will gain added relevance as research continues and new opportunities for optimizing treatment and enhancing outcomes emerge.

## UPMC Research

At the University of Pittsburgh Medical Center (UPMC) and the University of Pittsburgh, researchers have significantly expanded NGS capabilities. Molecular pathologists sequenced large regions of genome for 250 patients suffering from late-stage lung, colon, breast, and other common cancers. The program used the Personalized Cancer Mutation Panel (PCMP) that can identify 2,800 mutations in 50 key cancer genes. By analyzing these patients with advanced cancer who failed standard therapies, UPMC developed new therapeutic targets.

The organization also began offering NGS testing for patients with every cancer type and stage when there is clinical necessity. Currently over 12,000 diagnostic and prognostic molecular and genomic assays are conducted annually. For example, ThyroSeq®, UPMC's thyroid cancer NGS panel, provides simultaneous sequencing and detection in more than 1,000 hotspots of 14 thyroid cancer–related genes and for 42 types of gene fusions known to occur in thyroid cancer. Although most thyroid nodules are benign, thyroid cancer is the most common malignancy of endocrine organs, and its incidence is steadily growing in the United States and worldwide.[9] The use of the NGS thyroid panel following fine needle aspiration (FNA) allows for detection of genetic mutations associated with malignancy, which in turn affects clinical decisions related to surgery, administration of radioactive iodine, intensity of follow-up, and targeted therapies for advanced cancer.

In addition to thyroid cancer, solid tumor testing at UPMC provides a personalized molecular profile for individualized therapy, diagnosis, and prognosis for brain tumors, lung cancer, colorectal cancer, melanoma, parathyroid tumors, hepatocellular carcinoma, appendiceal tumors, and pancreatic cysts. An expanded cancer panel is also offered for most solid tumors and includes 50 genes tested by NGS technology. In addition, loss of heterozygosity (LOH) testing is available for patients with two tumors to determine whether the tumors represent two primary tumors or metastatic disease.

The use of NGS is driving many of the clinical trials now under way at UPMC. Currently, a hereditary colorectal tumor registry is collecting information regarding genetic makeup to diagnose, treat, and improve mortality in high-risk individuals. Another trial is under way to study the side effects of trastuzumab (Herceptin®), a targeted monoclonal antibody that blocks tumor growth, and to determine how well it works in treating older women with early breast cancer. Researchers are also evaluating the safety and potential effectiveness of a new treatment for advanced and recurrent melanoma involving the combination of ipilimumab (Yervoy®) and IFN-a2b before surgery and to test for biomarker studies in blood and/or tumor to better understand the disease, how to best treat it, and which patients should be treated with this combination.

## Clinical and Financial Considerations

NGS is less costly and time-consuming than previous genetic tests, but many practical issues remain in the effective use of advances in sequencing technology. More than 1,000 genomic

tests are currently available for more than 2,000 diseases,[10] with technology threatening to outpace data analysis and interpretation. The rapid pace of discovery prompted the federal government in 2012 to create a three-tiered, scientific- and evidence-based classification system for genomic testing. The three criteria for Tier 1 genomic tests are:

- Food and Drug Administration (FDA) label requires use of test to inform choice or dose of a drug;
- Centers for Medicare & Medicaid Services (CMS) covers testing; and
- Clinical practice guidelines based on systematic review supports testing.[11]

Genomic tests that fall into the second, "yellow" tier are less well defined; for example, systematic review finds insufficient evidence, but does not discourage use of test.[11] Third tier or "red" applications have evidence-based recommendations against their use.[11]

A total of 49 genomic applications are now classified as Tier 1 or "green" with a base of synthesized evidence supporting implementation into practice.[11] Thirty-seven of the applications in the Tier 1 category are oncology related — breast/ovarian, colorectal, gastric, and lung cancers; leukemia/lymphoma; and melanoma.[11] (See Table 1.)

Beyond the tiered classification system, evaluation of genomic tests is an ongoing challenge. Providers, payors, researchers, and NGS technology experts at a Boston Healthcare Associates and Cambridge Healthtech Institute symposium recently called for well-developed clinical trials, open sharing of databases about genetic variants, and strategies to help physicians make the best use of NGS data.[12] The ultimate aim of addressing these evidence gaps is to define and select which patients will benefit most from NGS testing (e.g., stage III or IV lung cancer patients versus all breast cancer patients).[12] Although the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group has sought to provide guidance on which genetic tests may or may not be supported by the evidence base (e.g., Lynch syndrome screening protocols are now widely accepted), the independent, nonfederal group has issued only nine recommendations since its inception in 2004.[13]

Discussion about clinical guidelines is particularly important given the national focus on health care costs and value. While DNA sequencing costs have dropped dramatically, costs for quality control, bioinformatics, and data analysis following initial data processing are significant.[1] For example, sequencing a genome may be possible for only a few thousand dollars, but the cost of interpretation could exceed six figures. Another cost consideration is the substantial patient education/communication that must be provided by genetic counselors.[14]

## Payor Challenges

NGS offers opportunities to better understand and treat cancer, but the emergent nature of the technology poses challenges for payors seeking to make informed coverage decisions. The FDA has yet to approve use of NGS sequencers on tumor samples or as companion diagnostics, and Medicare reimbursement policies and practices remain in flux.[14] In this uncertain environment, private and public payors alike are seeking information about clinical validity and clinical utility in order to make coverage decisions.[14]

The validity of NGS results, processed at laboratories that typically operate under Clinical Laboratory Improvement Amendments (CLIA) certification, is a concern for payors who seek to limit ineffective tests. Payors typically do not have the ability to independently evaluate the clinical validity of NGS tests, although the release of clinical guidelines by the American College of Medical Genetics and Genomics (ACMG) and molecular pathology accreditation standards by the College of American Pathologists (CAP) may address the need for standardization.[14] Clinical utility decisions are also complicated by different payor definitions of what data demonstrate clinical utility.

Payors seeking to make decisions related to personalized medicine frequently turn to health care technology assessment (HTA) organizations such as EGAPP and Blue Cross and Blue Shield Association's Center for Clinical Effectiveness (CCE) (formerly Technology Evaluation Center [TEC]) to make coverage decisions.[15] Payors also rely on guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). Many payors, particularly larger organizations, use more than one HTA for evaluation of clinical evidence for genomics.[15] Payors have been challenged, though, by a number of HTA shortcomings. A lack of availability of reviews of personalized medicine, HTA subscription costs, and inadequate consideration of cost-effectiveness and other nonclinical factors are among the chief concerns.[15]

## Pharmacy Utilization Management

Sequencing technology and the resulting personalized medicine hold the promise of making health care more efficient.[7,16] NGS tests performed though noninvasive or FNA techniques may eliminate the need for costly and unnecessary surgeries. NGS can also be used to identify the right drug, including a less expensive generic drug, for the right patient, and to provide disease control over the long term.[16] At the same time,

genomics has driven the trend toward costly specialty injectables and biologics. Eight of the top 10 drugs, according to sales estimates, are expected to be specialty products by 2016,[17] with hundreds of specialty cancer drugs in development.

Given the high cost of oncology therapies, which commonly surpass $10,000 per month, targeting therapies to a smaller subset of patients within a specific cancer offers opportunities for greater efficacy. Sequencing and other detailed characterizations of tumors and other cancer cells have demonstrated that there is far more heterogeneity between cancers within the same diagnosis than previously appreciated. In addition, the effectiveness and toxicity of chemotherapy and other treatments vary widely among patients due to heterogeneity in pharmacokinetics, radiation sensitivity, and other patient characteristics.

Stratifying diseases such as cancer is vital in choosing the correct therapy for each disease type and ensuring that the appropriate patients receive the most appropriate therapies.[7] Genomic stratification of cancer means a move away from a one-size-fits-most cytotoxic chemotherapy approach to a personalized strategy that employs molecular therapeutic drugs. Pharmacogenomics, or the effects of an individual's genetics on medication response or interactions, is also important in developing personalized cancer therapies. The goal of targeted therapies is to provide greater efficacy and lesser toxicity while avoiding ineffective therapies that are costly both to patients and to the health care system as a whole.[7]

Pharmacy utilization management is important in making treatment decisions that are tailored to a patient's genetic makeup and cancer-related mutations. Relevant oncology tests include screening to profile a patient's risk for cancer and diagnostics to identify cancer or disease type. Therapy management, either through prognostic or predictive tests, is then used to guide treatment decisions. Prognostic testing assesses tumor risk and stratifies disease by molecular subtype. Predictive tests indicate whether a treatment may be effective based on patient type, such as genetic variations of CYP2D6 that can affect the metabolism of tamoxifen (Nolvadex®) for breast cancer patients who would instead benefit from an aromatase inhibitor,[18] or tumor characteristics such as use of the biologic therapy trastuzumab (Herceptin®) in HER2-positive breast cancer patients.[19] Response monitoring is the third component of therapy management, focusing on tracking response to treatment (e.g., measuring BCR-ABL levels in chronic myeloid leukemia patients) to guide future therapy.

Personalized medicine also offers opportunities for preventive medicine that emphasizes wellness rather than disease treatment.[7] For example, one-time HER2 testing in advance of breast cancer therapy and KRAS testing in advance of colorectal cancer therapy are increasingly covered by payors.[20] One-time BRCA testing for breast cancer susceptibility genes, however, is not covered by most health plans, and new genomic test requirements from payors do not appear to be in the pipeline.[20] Although barriers to widespread use of genomic testing remain, the utilization of these diagnostic and prognostic procedures are likely to play a major role in the management of a variety of cancer types in the coming years.

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# With schizophrenia, choosing an antipsychotic individualized to patients' needs can be complex.[1]

Not actual patients.

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## INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension

### INDICATION

**Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.**

### IMPORTANT SAFETY INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.**

**Contraindication:** Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

**Cerebrovascular Adverse Events, Including Stroke:** Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

# Accessing long-acting injectables shouldn't be.

**Position Abilify Maintena® (aripiprazole) at parity with all long-acting injectables on your formulary. Offer the efficacy* and safety of oral aripiprazole for schizophrenia in a once-monthly formulation.[2,3,†]**

*Abilify Maintena significantly delayed the time to impending relapse vs placebo ($P<0.0001$) in a phase III, 52-week, double-blind, randomized-withdrawal clinical trial; Abilify Maintena (n=269) vs placebo (n=134).[3]

† Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials. In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

## IMPORTANT SAFETY INFORMATION *(continued)*

**Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including Abilify Maintena. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

**Tardive Dyskinesia (TD):** The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

ONCE-MONTHLY

400MG

Abilify Maintena®

(aripiprazole) for extended release injectable suspension

## IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension *(continued)*

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

**Orthostatic Hypotension:** Aripiprazole may cause orthostatic hypotension. Abilify Maintena should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

**Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

**Seizures/Convulsions:** Abilify Maintena should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

**Potential for Cognitive and Motor Impairment:** Abilify Maintena may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain Abilify Maintena does not affect them adversely.

**Body Temperature Regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with Abilify Maintena; use caution in patients at risk for aspiration pneumonia.

**Alcohol:** Advise patients to avoid alcohol while taking Abilify Maintena.

**Concomitant Medication:** Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the Abilify Maintena dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

**Most Commonly Observed Adverse Reaction:** Based on the placebo-controlled trial of Abilify Maintena in schizophrenia, the most commonly observed adverse reactions associated with the use of aripiprazole (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight (16.8% vs 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs 0.6%), and sedation (5.4% vs 1.2%).

**Injection Site Reactions:** In the data from the short-term, double-blind, placebo-controlled trial with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction (all reported as injection site pain) was 5.4% for patients treated with gluteal administered Abilify Maintena and 0.6% for placebo.

**Dystonia:** Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

**Pregnancy/Nursing:** Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is present in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on adjacent pages.

Otsuka
Otsuka America Pharmaceutical, Inc.

Lundbeck

**ABILIFY MAINTENA® (aripiprazole) for extended-release injectable suspension, for intramuscular use**

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details, please *see Full Prescribing Information and Medication Guide.*)

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

*See full prescribing information for complete boxed warning.*

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death**
- **ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis**

**INDICATIONS AND USAGE:** ABILIFY MAINTENA (aripiprazole) is indicated for the treatment of schizophrenia.

**CONTRAINDICATIONS:** ABILIFY MAINTENA is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole.

**WARNINGS AND PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

**Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, in oral aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with oral aripiprazole. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome:** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

**Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY MAINTENA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with ABILIFY MAINTENA drug discontinuation should be considered. However, some patients may require treatment with ABILIFY MAINTENA despite the presence of the syndrome.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/ diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

**Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes), who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

In a short-term, placebo-controlled randomized trial in adults with schizophrenia, the mean change in fasting glucose was +9.8 mg/dL (N=88) in the ABILIFY MAINTENA-treated patients and +0.7 mg/dL (N=59) in the placebo-treated patients. Table 1 shows the proportion of ABILIFY MAINTENA-treated patients with normal and borderline fasting glucose at baseline and their changes in fasting glucose measurements.

**Table 1: Proportion of Patients with Potential Clinically Relevant Changes in Fasting Glucose from a 12-Week Placebo-Controlled Monotherapy Trial in Adult Patients with Schizophrenia**

| | Category Change (at least once) from Baseline | Treatment Arm | n/N[a] | % |
|---|---|---|---|---|
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | ABILIFY MAINTENA | 7/88 | 8.0 |
| | | Placebo | 0/75 | 0.0 |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | ABILIFY MAINTENA | 1/33 | 3.0 |
| | | Placebo | 3/33 | 9.1 |

[a] N = the total number of subjects who had a measurement at baseline and at least one post-baseline result. n = the number of subjects with a potentially clinically relevant shift.

**Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Table 2 shows the proportion of adult patients from one short-term, placebo- controlled randomized trial in adults with schizophrenia taking ABILIFY MAINTENA, with changes in total cholesterol, fasting triglycerides, fasting LDL cholesterol and HDL cholesterol.

**Table 2: Proportion of Patients with Potential Clinically Relevant Changes in Blood Lipid Parameters From a 12-Week Placebo-Controlled Monotherapy Trial in Adults with Schizophrenia**

| | Treatment Arm | n/N[a] | % |
|---|---|---|---|
| **Total Cholesterol** | ABILIFY MAINTENA | 3/83 | 3.6 |
| Normal to High (<200 mg/dL to ≥240 mg/dL) | Placebo | 2/73 | 2.7 |
| Borderline to High (200~<240 mg/dL to ≥240 mg/dL) | ABILIFY MAINTENA | 6/27 | 22.2 |
| | Placebo | 2/19 | 10.5 |
| Any increase (≥40 mg/dL) | ABILIFY MAINTENA | 15/122 | 12.3 |
| | Placebo | 6/110 | 5.5 |
| **Fasting Triglycerides** | ABILIFY MAINTENA | 7/98 | 7.1 |
| Normal to High (<150 mg/dL to ≥200 mg/dL) | Placebo | 4/78 | 5.1 |
| Borderline to High (150~<200 mg/dL to ≥200 mg/dL) | ABILIFY MAINTENA | 3/11 | 27.3 |
| | Placebo | 4/15 | 26.7 |
| Any increase (≥50 mg/dL) | ABILIFY MAINTENA | 24/122 | 19.7 |
| | Placebo | 20/110 | 18.2 |
| **Fasting LDL Cholesterol** | ABILIFY MAINTENA | 1/59 | 1.7 |
| Normal to High (<100 mg/dL to ≥160 mg/dL) | Placebo | 1/51 | 2.0 |
| Borderline to High (100~<160 mg/dL to ≥160 mg/dL) | ABILIFY MAINTENA | 5/52 | 9.6 |
| | Placebo | 1/41 | 2.4 |
| Any increase (≥30 mg/dL) | ABILIFY MAINTENA | 17/120 | 14.2 |
| | Placebo | 9/103 | 8.7 |
| **HDL Cholesterol** | ABILIFY MAINTENA | 14/104 | 13.5 |
| Normal to Low (≥40 mg/dL to <40 mg/dL) | Placebo | 11/87 | 12.6 |
| Any decrease (≥20 mg/dL) | ABILIFY MAINTENA | 7/122 | 5.7 |
| | Placebo | 12/110 | 10.9 |

[a] N = the total number of subjects who had a measurement at baseline and at least one post-baseline result. n = the number of subjects with a potentially clinically relevant shift.

**Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

In one short-term, placebo-controlled trial with ABILIFY MAINTENA, the mean change in body weight at Week 12 was +3.5 kg (N=99) in the ABILIFY MAINTENA-treated patients and +0.8 kg (N=66) in the placebo-treated patients.

Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in a short-term, placebo-controlled trial with ABILIFY MAINTENA.

**Table 3: Percentage of Patients From a 12-Week Placebo-Controlled Trial in Adult Patients with Schizophrenia with Weight Gain ≥7% of Body Weight**

| | Treatment Arm | N[a] | Patients n (%) |
|---|---|---|---|
| **Weight gain ≥7% of body weight** | ABILIFY MAINTENA | 144 | 31 (21.5) |
| | Placebo | 141 | 12 (8.5) |

[a] N = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Orthostatic Hypotension:** ABILIFY MAINTENA may cause orthostatic hypotension, perhaps due to its $\alpha$1-adrenergic receptor antagonism. In the short-term, placebo-controlled trial in adults with schizophrenia, the adverse event of presyncope was reported in 1/167 (0.6%) of patients treated with ABILFY MAINTENA, while syncope and orthostatic hypotension were each reported in 1/172 (0.6%) of patients treated with placebo. During the stabilization phase of the randomized-withdrawal (maintenance) study, orthostasis-related adverse events were reported in 4/576 (0.7%) of patients treated with ABILIFY MAINTENA, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the short-term placebo-controlled trial, there were no patients in either treatment group with a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values). During the stabilization phase of the randomized-withdrawal (maintenance) study, the incidence of significant orthostatic change in blood pressure was 0.2% (1/575).

**Leukopenia, Neutropenia, and Agranulocytosis:** In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY MAINTENA. Agranulocytosis has also been reported

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and a history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm$^3$) and follow their WBC counts until recovery.

**Seizures:** As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

**Potential for Cognitive and Motor Impairment:** ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA does not affect them adversely.

**Body Temperature Regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

**ADVERSE REACTIONS:** The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis Use
- Neuroleptic Malignant Syndrome
- Metabolic Changes
- Leukopenia, Neutropenia, and Agranulocytosis
- Potential for Cognitive and Motor Impairment
- Dysphagia
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis
- Tardive Dyskinesia
- Orthostatic Hypotension
- Seizures
- Body Temperature Regulation

**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.

**Safety Database of ABILIFY MAINTENA and Oral Aripiprazole:** Oral aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications, and who had approximately 8,578 patient-years of exposure to oral aripiprazole. A total of 3,901 patients were treated with oral aripiprazole for at least 180 days, 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment for at least 720 days.

ABILIFY MAINTENA has been evaluated for safety in 2,188 adult patients in clinical trials in schizophrenia, with approximately 2,646 patient-years of exposure to ABILIFY MAINTENA. A total of 1,230 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 935 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and open-label studies. The safety data presented below are derived from the 12-week double-blind placebo-controlled study of ABILIFY MAINTENA in adult patients with schizophrenia.

**Adverse Reactions with ABILIFY MAINTENA:** *Most Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials in Schizophrenia*

*Based on the placebo-controlled trial of ABILIFY MAINTENA in schizophrenia, the most commonly observed adverse reactions associated with the use of aripiprazole in patients (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight (16.8% vs 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs 0.6%) and sedation (5.4% vs 1.2%).*

*Commonly Reported Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials in Schizophrenia*

*The following findings are based on the double-blind, placebo-controlled trial that compared ABILIFY MAINTENA 400 mg or 300 mg to placebo in patients with schizophrenia. Table 4 lists the adverse reactions reported in 2% or more of ABILIFY MAINTENA-treated subjects and at a greater proportion than in the placebo group.*

**Table 4: Adverse Reactions in ≥2% of ABILIFY MAINTENA-Treated Adult Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial[a]**

| | Percentage of Patients Reporting Reaction[a] | |
|---|---|---|
| System Organ Class<br>Preferred Term | ABILIFY MAINTENA<br>(n=167) | Placebo<br>(n=172) |
| **Gastrointestinal Disorders** | | |
| Constipation | 10 | 7 |
| Dry Mouth | 4 | 2 |
| Diarrhea | 3 | 2 |
| Vomiting | 3 | 1 |
| Abdominal Discomfort | 2 | 1 |
| **General Disorders and Administration Site Conditions** | | |
| Injection Site Pain | 5 | 1 |
| **Infections and Infestations** | | |
| Upper Respiratory Tract Infection | 4 | 2 |
| **Investigations** | | |
| Increased Weight | 17 | 7 |
| Decreased Weight | 4 | 2 |
| **Musculoskeletal And Connective Tissue Disorders** | | |
| Arthralgia | 4 | 1 |
| Back Pain | 4 | 2 |
| Myalgia | 4 | 2 |
| Musculoskeletal Pain | 3 | 1 |
| **Nervous System Disorders** | | |
| Akathisia | 11 | 4 |
| Sedation | 5 | 1 |
| Dizziness | 4 | 2 |
| Tremor | 3 | 1 |

**Table 4: Adverse Reactions in ≥2% of ABILIFY MAINTENA-Treated Adult Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial[a]**

| | Percentage of Patients Reporting Reaction[a] | |
|---|---|---|
| System Organ Class<br>Preferred Term | ABILIFY MAINTENA<br>(n=167) | Placebo<br>(n=172) |
| **Respiratory, Thoracic And Mediastinal** | | |
| Nasal Congestion | 2 | 1 |

[a]This table does not include adverse reactions which had an incidence equal to or less than placebo.

*Other Adverse Reactions Observed During the Clinical Trial Evaluation of ABILIFY MAINTENA:* The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

*Blood and Lymphatic System Disorders: rare* - thrombocytopenia

*Cardiac Disorders:* infrequent - tachycardia, *rare* - bradycardia, sinus tachycardia

*Endocrine Disorders: rare* - hypoprolactinemia

*Eye Disorders: infrequent* - vision blurred, oculogyric crisis

*Gastrointestinal Disorders: infrequent* - abdominal pain upper, dyspepsia, nausea, *rare* - swollen tongue

*General Disorders and Administration Site Conditions: frequent* - fatigue, injection site reactions (including erythema, induration, pruritus, injection site reaction, swelling, rash, inflammation, hemorrhage), *infrequent* - chest discomfort, gait disturbance, *rare* - irritability, pyrexia

*Hepatobiliary Disorders: rare* - drug induced liver injury

*Immune System Disorders: rare* - drug hypersensitivity

*Infections and Infestations: rare* - nasopharyngitis

*Investigations: infrequent* - blood creatine phosphokinase increased, blood pressure decreased, hepatic enzyme increased, liver function test abnormal, electrocardiogram QT-prolonged, *rare* - blood triglycerides decreased, blood cholesterol decreased, electrocardiogram T-wave abnormal

*Metabolism and Nutrition Disorders: infrequent* - decreased appetite, obesity, hyperinsulinemia

*Musculoskeletal and Connective Tissue Disorders: infrequent* - joint stiffness, muscle twitching, *rare* - rhabdomyolysis

*Nervous System Disorders: infrequent* - cogwheel rigidity, extrapyramidal disorder, hypersomnia, lethargy, *rare* - bradykinesia, convulsion, dysgeusia, memory impairment, oromandibular dystonia

*Psychiatric Disorders: frequent* - anxiety, insomnia restlessness, *infrequent* - agitation, bruxism, depression, psychotic disorder, suicidal ideation, *rare* - aggression, hypersexuality, panic attack

*Renal and Urinary Disorders: rare* - glycosuria, pollakiuria, urinary incontinence

*Vascular Disorders: infrequent* - hypertension

*Demographic Differences:* An examination of population subgroups was performed across demographic subgroup categories for adverse reactions experienced by at least 5% of aripiprazole IM depot subjects at least twice rate of the placebo (i.e., increased weight, akathisia, injection site pain, and sedation) in the double-blind placebo-controlled trial. This analysis did not reveal evidence of differences in safety differential adverse reaction incidence on the basis of age, gender, or race alone; however, there were few subjects ≥65 years of age.

*Injection Site Reactions of ABILIFY MAINTENA:* In the data from the short-term, double-blind, placebo-controlled trial with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction (all reported as injection site pain) was 5.4% for patients treated with gluteal administered ABILIFY MAINTENA and 0.6% for placebo. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) approximately one hour after injection was 7.1 (SD 14.5) for the first injection and 4.8 (SD 12.4) at the last visit in the double-blind, placebo-controlled phase.

*Extrapyramidal Symptoms (EPS):* In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY MAINTENA-treated patients was 9.6% vs. 5.2% for placebo. The incidence of akathisia-related events for ABILIFY MAINTENA-treated patients was 11.5% vs. 3.5% for placebo.

*Dystonia:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of dystonia was 1.8% for ABILIFY MAINTENA vs. 0.6% for placebo.

*Neutropenia:* In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of neutropenia (absolute neutrophil count ≤1.5 thous/µL) for ABILIFY MAINTENA-treated patients was 5.7% vs. 2.1% for placebo. An absolute neutrophil count of <1 thous/µL (i.e. 0.95 thous/µL) was observed in only one patient on ABILIFY MAINTENA and resolved spontaneously without any associated adverse events.

*Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole*

The following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for Abilify Maintena:

*Cardiac Disorders:* palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia, atrial flutter, supraventricular tachycardia, ventricular tachycardia

*Eye Disorders:* photophobia, diplopia, eyelid edema, photopsia

*Gastrointestinal Disorders:* gastroesophageal reflux disease, swollen tongue, esophagitis, pancreatitis, stomach discomfort, toothache

*General Disorders and Administration Site Conditions:* asthenia, peripheral edema, chest pain, face edema, angioedema, hypothermia, pain

*Hepatobiliary Disorders:* hepatitis, jaundice

*Immune System Disorders:* hypersensitivity Injury, Poisoning, and Procedural Complications: heat stroke

*Investigations:* blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, blood lactate dehydrogenase increased, glycosylated hemoglobin increased

*Metabolism and Nutrition Disorders:* anorexia, hyponatremia, hypoglycemia, polydipsia, diabetic ketoacidosis

*Musculoskeletal and Connective Tissue Disorders:* muscle rigidity, muscular weakness, muscle tightness, decreased mobility, rhabdomyolysis, musculoskeletal stiffness, pain in extremity, muscle spasms

*Nervous System Disorders:* coordination abnormal, speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia, choreoathetosis

*Psychiatric Disorders:* loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation, catatonia, sleep walking

*Renal and Urinary Disorders:* urinary retention, polyuria, nocturia

*Reproductive System and Breast Disorders:* menstruation irregular, erectile dysfunction, amenorrhea, breast pain, gynecomastia, priapism

*Respiratory, Thoracic, and Mediastinal Disorders:* nasal congestion, dyspnea, pharyngolaryngeal pain, cough

*Skin and Subcutaneous Tissue Disorders:* rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhidrosis, pruritus, photosensitivity reaction, alopecia, urticaria

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of oral aripiprazole or ABILIFY MAINTENA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm) and blood glucose fluctuation.

**DRUG INTERACTIONS: Drugs Having Clinically Important Interactions with ABILIFY MAINTENA**

Table 5: Clinically Important Drug Interactions with ABILIFY MAINTENA:

| Concomitant Drug Name or Drug Class | Clinical Rationale | Clinical Recommendation |
|---|---|---|
| Strong CYP3A4 Inhibitors (e.g., ketoconazole) or strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) | The concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole. | With concomitant use of ABILIFY MAINTENA with a strong CYP3A4 inhibitor or CYP2D6 inhibitor for more than 14 days, reduce the ABILIFY MAINTENA dosage. |
| Strong CYP3A4 Inducers (e.g., carbamazepine) | The concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole. | Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days. |
| Antihypertensive Drugs | Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents. | Monitor blood pressure and adjust dose accordingly. |
| Benzodiazepines (e.g., lorazepam) | The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone. | Monitor sedation and blood pressure. Adjust dose accordingly. |

**Drugs Having No Clinically Important Interactions with ABILIFY MAINTENA:** Based on pharmacokinetic studies with oral aripiprazole, no dosage adjustment of ABILIFY MAINTENA is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin), or CYP3A4 (e.g., dextromethorphan) when co-administered with ABILIFY MAINTENA. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY MAINTENA.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** *Pregnancy Category C: Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

*Risk Summary:* Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women.

Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre-and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Clinical Considerations:* Fetal/Neonatal Adverse Reactions: Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including oral aripiprazole) during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates exhibiting extrapyramidal or withdrawal symptoms.

**Nursing Mothers:** ABILIFY is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from ABILIFY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** ABILIFY MAINTENA has not been studied in children 18 years of age or younger. However, juvenile animal studies have been conducted in rats and dogs.

**Juvenile Animal Studies:** Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, 40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

**Geriatric Use:** Clinical studies of ABILIFY did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data have not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In single-dose and multiple-dose pharmacokinetic studies, there was no detectable age effect in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. No dosage adjustments are recommended based on age alone. ABILIFY MAINTENA is not approved for the treatment of patients with psychosis associated with Alzheimer's disease.

**CYP2D6 Poor Metabolizers:** Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM).

**Hepatic and Renal Impairment:** No dosage adjustment for ABILIFY MAINTENA is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute).

**Other Specific Populations:** No dosage adjustment for ABILIFY MAINTENA is required on the basis of a patient's sex, race, or smoking status.

**CYP2D6 Poor Metabolizers:** Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations.

**OVERDOSAGE: Human Experience:** The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

**Management of Overdosage: In case of overdosage, call the Poison Control Center immediately at 1-800-222-1222.**

**To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda. gov/medwatch.**

For more information about ABILIFY MAINTENA, visit www.abilifymaintena.com.

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# Opioid Dependence: A Chronic Disease
## Maintenance Medical Treatment Improves Outcomes, Reduces Costs

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The United States is in the midst of an epidemic of opioid abuse and misuse, with more than 4.5 million people using prescription painkillers every year for nonmedical reasons; an estimated 2 million people dependent on or addicted to prescription pain relievers; and deaths from misuse of prescription narcotics exceeding those from illegal drugs (See Figure 1).[1] The numbers are far higher in the Medicaid population, in which 87 per 10,000 beneficiaries are estimated to be abusing opioids, nearly 10 times more than those in commercial insurance plans.[2]

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In addition, there was a 37 percent increase in opioid abuse between 2008 and 2010 in the commercially insured population.[3]

Opioid dependency and prescription drug abuse is also a growing problem among Medicare beneficiaries. A retrospective analysis of claims from Medicare managed care plans found the six-month prevalence of diagnosed opioid abuse more than doubled between 2008 and 2010, from 3.17 to 6.35 (per 1,000 beneficiaries), even with no significant increase in prescriptions.[3]

The economic impact of opioid abuse is significant, costing insurers at least $72.5 billion a year.[4] An analysis of medical costs for opioid abusers found annual medical costs $14,054 higher in a commercially insured population and $6,650 higher in the Medicaid population than for nonabusers (P <.01 for both). Abusers also had a substantially higher prevalence of comorbidities.[2] Opioid misuse also puts an increased burden on employers, costing approximately $1.71 per member per month.[5]

The implementation of the Affordable Care Act (ACA) may dramatically increase the number of individuals seeking medical care for drug dependence as millions gain coverage through state Medicaid plans and commercial insurers.

The ACA builds on the Mental Health Parity and Addiction Equity Act of 2008, and defines treatment for substance use disorders as an essential health benefit in all insurance plans sold on the exchanges and all Medicaid expansion plans, establishing parity between mental health/substance abuse benefits and medical/surgical benefits.[6,7]

Thus, it is imperative that health plans and prescription drug providers (PDPs) identify best practices for treating opioid dependence and addiction.

## Substance Abuse as a Chronic Condition

Substance abuse disorders like opioid dependency are chronic conditions requiring long-term medical and psychosocial maintenance treatment.[8,9] Indeed, without maintenance therapy, relapse rates for substance abuse are similar to those of other chronic conditions like diabetes, asthma, and hypertension, and, like these conditions, can be managed long-term.[8] Managing the chronic illness is the goal, rather than striving for a complete cure.

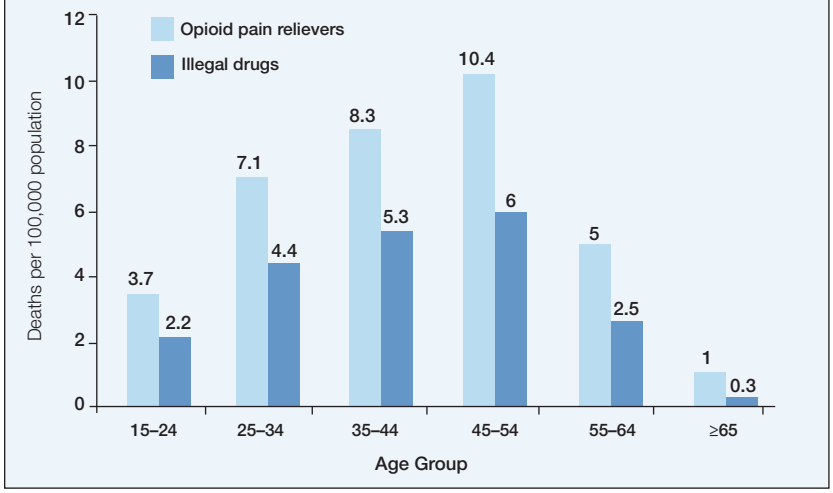
However, despite the overwhelming prevalence of evidence as to the chronic nature of opioid addiction and the availability of several effective treatments, opioid dependence is still managed as an acute medical condition. The goal is to wean patients off the drugs, with little attention paid to reducing relapse with maintenance therapy. Many health plans and state Medicaid programs often have significant barriers in place that restrict the use of medication-assisted therapy (MAT) for opioid dependence.[8]

As McLellan et al noted in a study highlighting the chronic nature of drug dependence, when patients with chronic physical health conditions stop their treatments and relapse, it is "considered evidence of the effectiveness of those treatments and the need to retain patients." Yet when patients with substance abuse diagnoses relapse after they are discharged or stop treatment, the treatment is considered to have failed.[9] The authors also concluded that if medications for hypertension and similar conditions were as difficult to prescribe as those for substance abuse, few physicians would prescribe them as maintenance medications.

## Medical Treatments for Opioid Dependence

Five medications are typically used for the maintenance treatment of opioid addiction/dependence (See Table 1): methadone; three buprenorphine/naloxone products: Suboxone® Film, Zubsolv®, and Bunavail™; and the extended-release, injectable Vivitrol® (naltrexone).[8] Additionally, oral naltrexone is effective for some patients, and buprenorphine monotherapy is frequently used during the induction period and to treat pregnant women dependent on opiates.

**Figure 1: Deaths from Opioid Pain Relievers Exceed Those from All Illegal Drugs**




Source: Overdoses of prescription opioid pain relievers — United States, 1999–2008. *Morbidity and Mortality Weekly Report.* 2011;60(43):1487-1492.

Studies also find that MAT is more effective at managing opioid addiction and dependence and retaining patients in treatment than nonmedical approaches. It is also more cost-effective,[17-19] with one study finding that every dollar spent on treatment results in a savings of $1.80.[20]

### Medicare and Prescription Pain Reliever Abuse

Prescription opioids accounted for about 5 percent of all Medicare Part D drug costs in 2011. Among the 10 million beneficiaries without a cancer diagnosis or not in hospice, the top 5 percent of users accounted for 69 percent of total spending on opioids, filling an average of 23 prescriptions a year, a third of them from four or more prescribers at three or more pharmacies.[10]

The Centers for Medicare & Medicaid Services (CMS) instituted new drug utilization review (DUR) requirements in 2013 for Medicare Prescription Drug Plans (PDPs) in an effort to address the growing misuse of prescription pain relievers. The requirements dictate that PDPs have retrospective drug utilization review systems, policies, and procedures in place to identify inappropriate use of opioids and other prescription drugs. This policy also enables PDPs to address the problem directly with the beneficiary and, in certain instances, to deny coverage for the drug at the point of service.[11]

In June 2015, new regulations will require that prescribers enroll with the Medicare program in order to write Part D–eligible prescriptions. In addition, CMS announced it would begin analyzing Part D prescription drug data to assess fraud and abuse risk of prescribers and pharmacies, and would revoke the Medicare privileges of abusive prescribers.[10]

**Table 1 Approved Maintenance Medications for Opioid Dependence/Addiction**

| Medication (Brand/Generic) | Indication | Available Strengths | Form | Cost (WAC) |
|---|---|---|---|---|
| Suboxone Film (buprenorphine/naloxone)[14] | Induction and maintenance therapy | 2 mg/0.5 mg<br>4 mg/1 mg<br>8 mg/2 mg<br>12 mg/3 mg<br><br>Frequency: Daily | Sublingual film | $4–$14 per film |
| Bunavail (buprenorphine/naloxone)[12,13] | Maintenance therapy | 2.1 mg/0.3 mg<br>4.2 mg/0.7 mg<br>6.3 mg/1 mg<br><br>Frequency: Daily | Buccal film | $7–$14 per film |
| Zubsolv (buprenorphine/naloxone)[13] | Maintenance therapy | 1.4 mg/0.36 mg<br>5.7 mg/1.4 mg<br><br>Frequency: Daily | Sublingual tablet | $3.50–$7 per tablet |
| Buprenorphine/Naloxone HCl (generic tablets) | Maintenance therapy | 2 mg/0.5 mg<br>8 mg/2 mg<br><br>Frequency: Daily | Sublingual tablet | $3.75–$8.35 per tablet |
| Subutex (buprenorphine) | Induction* | 2 mg<br>8 mg<br><br>Frequency: Daily | Sublingual tablet | $2.50–$4.67 per tablet |
| Vivitrol (naltrexone)[15] | Maintenance therapy | 380 mg<br><br>Frequency: Monthly | Injectable | $1,271 per month |
| Dolophine, Methadose, Methadose Sugar-Free, Diskets (methadone)[16] | Maintenance therapy | 5 mg tablets<br>10 mg tablets<br>40 mg diskets<br>5 mg/5 mL solution<br>10 mg/5 mL solution<br>10 mg/mL solution<br><br>Frequency: Daily | Liquid, tablets, soluble tablets, and liquid concentrate | $0.25–$0.50 per 5 mg–40 mg dose |

*May be used as maintenance therapy in pregnant patients and those with an allergy to naloxone

A 2011 analysis of a large commercial insurance data set involving 13,316 patients found those who received MAT for opioid dependence had significantly fewer hospital admissions for detoxification or rehabilitation than those who did not receive any medication. They also had significantly fewer opioid- and non-opioid-related inpatient admissions, and significantly lower medical costs overall, despite higher pharmacy costs.[21] Another study found lower mortality rates over 10 years in individuals who received MAT for more than seven days compared to those receiving only induction therapy.[22]

Maintenance therapy also results in higher rates of recovery. One study of 53 patients who received buprenorphine/naloxone therapy for two to five years found that 38 percent of subjects were retained in the study for two years and 91 percent of urine samples were opioid negative.[23] Another study evaluating 176 patients receiving the drug for 18 months found they were less likely to report using any substance and more likely to be employed.[24]

Switching patients from buprenorphine alone to a buprenorphine/naloxone combination can also improve outcomes. One study assessed 78 patients who were switched from buprenorphine after a median of 10 years of treatment to a biweekly buprenorphine/naloxone combination. Half the patients had no clinically relevant problems with switching to the combination drug, which effectively managed withdrawal symptoms in 78.1 percent. Seventy-eight percent of patients reported improved psychosocial functioning, and approximately 85 percent tested negative for opioids during the study. In addition, significantly more

A 2011 analysis of a large commercial insurance data set involving 13,316 patients found those who received MAT for opioid dependence had significantly fewer hospital admissions for detoxification or rehabilitation than those who did not receive any medication. They also had significantly fewer opioid- and non-opioid-related inpatient admissions, and significantly lower medical costs overall, despite higher pharmacy costs.[21]

patients reported satisfaction with the combination therapy compared to their previous monotherapy ($P < 0.001$). The combination therapy, while costing more than buprenorphine monotherapy, was more cost-effective overall, partially due to reduction in monitoring.[25]

Another study comparing costs between methadone, buprenorphine, or buprenorphine/naloxone found all three were equally cost-effective.[26]

Treatment with Vivitrol and other naltrexone products may be a consideration for some patients. As with all treatments for opioid dependence, prescription therapy must be accompanied by appropriate counseling for patients determined to be candidates for treatment with naltrexone, by experienced prescribers. Specifically, patients should have stopped taking opioids or opioid-containing medications seven to 14 days prior to beginning therapy. Patients should demonstrate an understanding of the risk associated with resuming opioid use while on Vivitrol, naltrexone-containing products, or other medications for treatment of opioid dependency.

## Barriers to Acute and Maintenance Therapy for Opioid Addiction/Dependence

Despite the efficacy and cost-effectiveness of antiaddiction medications, Medicaid and commercial insurers place significant restrictions on their use. A 2013 survey of 50 state Medicaid programs and 30 commercial insurers commissioned by the American Society of Addiction Medicine (ASAM) found that most Medicaid plans covered just one nonmethadone formulation, while 17 did not cover methadone. On the commercial side, just 23 percent of plans covered more than one medication. Sixty-six percent covered Vivitrol, typically as a specialty drug on tier 4; about half covered Suboxone, most as a tier 3 drug; and none covered methadone treatment.[27]

Restrictions on the coverage of long-term antiaddiction therapies are largely due to the lack of practice guidelines, cost, concerns about overutilization, and lack of knowledge about the benefits of continued maintenance therapy.

In addition, few commercial or Medicaid plans covered any kind of clinical treatment or counseling to accompany medical treatment.[27]

Overall, the authors of the aforementioned survey of state Medicaid programs and commercial insurers concluded that medications to treat opioid addiction are "grossly underutilized in the public sector" as a result of numerous barriers. These include lack of coverage, treatment duration or dosage limitations, prior authorization and step therapy requirements, and limits on who can prescribe the medications.[27] These barriers, in turn, lead to unclear coverage, high out-of-pocket costs, and limitations on long-term use. For instance, the authors noted that one commercial plan only covered Suboxone for acute withdrawal, not maintenance therapy.

Within the practice setting, physicians report other barriers to prescribing MAT, including lack of training and institutional support, time constraints during patient visits, financial issues, lack of confidence in their ability to manage opioid addiction/dependence, and lack of mental health and counseling services.[28-30]

## Conclusion

The country's epidemic of opioid abuse, dependence, and addiction shows no sign of slowing. The death rate from overdoses of prescription pain relievers in people under

65 is now comparable to deaths from motor vehicle accidents.[31]

The epidemic is already costing the U.S. health care system $72.5 billion annually, a figure that will substantially increase as millions of Americans gain commercial insurance and Medicaid coverage under the ACA, and as more Americans age into Medicare, which is beginning to experience its own increase in opioid addiction/dependence and overdoses.

Opioid dependence, often viewed a character flaw, is actually a chronic disease. As such, it should be treated as a chronic disease with ongoing medication and lifestyle management. There are several effective medications available for long-term therapy, which are more effective than nonmedical approaches as well as cost-effective.

However, health plans, including state Medicaid programs, limit the availability of MAT and have several barriers in place that restrict the use of antiaddiction medications, including prior authorization requirements, step therapy, high copayments, and limits on dosage and duration.

State and federal agencies, as well as commercial health plans, need to evaluate current restrictions on access to MAT and develop policies and procedures to manage patients with opioid dependence as they would manage any other patient with a chronic disease.

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# Multiple Sclerosis: Weighing Treatment Options and Assessing Risk Versus Benefit

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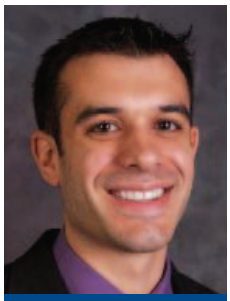

Sam Leo, PharmD

Multiple sclerosis (MS) is characterized as a progressive inflammatory disease of the central nervous system that severely damages myelin, an insulating coating around nerve cells, resulting in neurological dysfunction and disability.[1] There are four clinical types of MS: relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), progressive-relapsing multiple sclerosis (PRMS), and primary-progressive multiple sclerosis (PPMS).[1] The majority of patients, approximately 85 percent, are initially diagnosed at onset with RRMS, which can be described as clearly defined attacks, often called relapses, of deteriorating neurologic function.[1] SPMS is the phase that follows RRMS, as the disease gradually changes to a more progressive phase characterized by nerve damage or loss. An estimated 50 percent of patients with RRMS transition to SPMS within 10 years of the initial diagnosis.[2] PRMS is known as the least common of the four disease subtypes, occurring in approximately 5 percent of MS patients in which the worsening neurologic dysfunction is amplified.[2] Lastly, PPMS is described as a steady worsening of neurologic functioning, without any clear periods of relapses or remission, representing 10 percent of MS patients.[2]

Epidemiologists have discovered that factors such as gender, genetics, age, geographical location, and ethnic background could be potential causes of MS.[2] Currently, approximately 2.5 million people worldwide are diagnosed with MS, usually between the ages of 20 and 50.[2] It is estimated that 400,000 patients are afflicted with MS in the United States, and that approximately 200 new cases are diagnosed weekly.[2] Within the United States, the average person has an estimated 0.1 percent chance of developing MS.[2] The risk of being diagnosed with MS rises to 2.5 to 5 percent for first-degree relatives of a person with MS; however, an identical twin of someone with MS has a 25 percent chance of developing MS.[2] Adelman et al reviewed published studies assessing the annual cost per MS patient in the United States and found studies reported direct and indirect costs

ranging from $8,528 to $54,244 per patient per year in 2011 dollars, and that costs are expected to continue to increase annually; prescription medications were associated with the majority of direct costs.[3] In addition, health care costs related to MS are estimated to be more than $10 billion annually in the United States.[4]

## Lack of Clinical Guidelines

The treatment of MS is very complex, and involves management of the disease progression as well as symptoms. There is not a single treatment that works best for every patient; the treatment that is selected is based on a case-by-case evaluation and tailored to the individual patient. This is based on disease progression, patient symptoms, physician and patient assessment of treatment options, as well as patient out-of-pocket costs. Complicating therapeutic decisions is the lack of clinical guidelines to support a streamlined approach in the treatment of MS. State neurology societies do not collaborate with the American Academy of Neurology (AAN). This fragmentation between state societies and the AAN has resulted in few consensus guidelines regarding the use of disease-modifying therapies (DMTs) and symptom management.[5] In addition, there is a lack of objective, universally accepted quality metrics available to which physicians and payors can refer.[5] Additionally, the complexity of treating MS, the unpredictability of the disease, and necessary variations in treatment make measuring success in treating MS difficult.

The Schumacher Criteria from 1965 was initially used by physicians to aid in the diagnosis of MS.[4] The criteria consisted of the patient having an age range between 10 and 50 years and the presence of objective abnormalities upon examination, which are now outdated.[4] The McDonald Criteria, from the International Panel on the Diagnosis of Multiple Sclerosis, is a set of diagnostic criteria for MS that integrate the clinical characteristics alone or in combination with findings of an MRI.[4] Revisions to the criteria were made in 2005 and most recently in 2010 to reflect that a physician can make an earlier MS diagnosis based on the results of an MRI and clinical progression of the disease.[4] The need for updating guidelines remains. The 2010 update addressed the diagnosis of MS, but updated treatment guidelines to support the effective treatment of this progressive and complex condition are necessary.

## Evolving MS Landscape — Prescribing Trends

The MS landscape has evolved over time. According to the Consortium of Multiple Sclerosis Centers, in the mid 1990s care patterns changed for MS patients, "from symptomatic, fragmented, and episodic crisis intervention to a more intense focus on treatments and quality of care. Patients experience a wide range of symptoms throughout the course of the disease, creating a strong need for a dynamic approach to appropriate and comprehensive care."[6] The addition of DMTs is most effective early in the treatment of MS, and includes immunomodulatory, anti-inflammatory drugs, and immunosuppressive drugs which decrease neurological damage and progression of disability.[7] There are currently three oral DMTs approved by the FDA: Gilenya® (fingolimod), Aubagio® (teriflunomide), and Tecfidera® (dimethyl fumarate).[4]

Gilenya, the first oral DMT formulation, was approved by the FDA in September 2010.[8] Gilenya is used to treat relapsing forms of MS, helping to slow down the physical

"Patients experience a wide range of symptoms throughout the course of the disease, creating a strong need for a dynamic approach to appropriate and comprehensive care."[6]

problems that MS causes.[8] The results of a two-year, randomized, placebo-controlled phase 3 study indicated that the annualized relapse rate was reduced 54 to 60 percent in patients being treated, depending on the dose; these results were supported by improvements in MRI measurements of disease activity, which included reductions in the number of new or enlarging T2-weighted lesions.[8]

Aubagio was approved by the FDA in September 2012 for the treatment of RRMS.[9] In one clinical study, Aubagio reduced relapses by 42.6 percent for patients taking the 14 mg dose, and 37.2 percent for patients taking the 7 mg dose compared to placebo over the course of 108 weeks.[9]

Lastly, Tecfidera, formerly known as BG-12, was approved by the FDA in 2013 for patients with relapsing forms of MS.[10] Based on one clinical trial, Tecfidera reduced the number of annual relapse rates by 44 percent as compared to placebo.[10]

Lemtrada™ (alemtuzumab) was approved by the FDA in December 2014 for patients with relapsing forms of MS.[11] Lemtrada is to be given as an intravenous infusion for five consecutive days to start, and then for three days one year later.[11] However, due to its safety profile, Lemtrada therapy is recommended to be reserved for patients who have had an inadequate response to two or more MS therapies.[11] Two studies evaluating Lemtrada 12 mg in patients with relapsing-remitting MS suggest that Lemtrada significantly reduced the annualized relapse rate compared with interferon beta.[11] Although Lemtrada shows promising efficacy in relapsing-remitting MS patients, there are conditions that prescribers and patients need to understand fully before initiating treatment with Lemtrada. Lemtrada, due to its direct effect on one's immune system, is contraindicated in patients who are infected with human immunodeficiency virus (HIV).[11] Lemtrada may also cause serious side effects including cytokine release syndrome, melanoma, thyroid cancer, and lymphoma. For maximum safety, Lemtrada is managed under a Risk Evaluation and Mitigation Strategy (REMS) program as required by the FDA as a condition of the drug's approval.[11] A patient support program, MS One to One, is available to support patients with MS being treated with Lemtrada and to assist with enrollment in REMS.[11] Lemtrada's long-lasting effects are clinically significant and may improve patient compliance with therapy, however, it requires careful and constant monitoring for side effects. Therefore, physicians and patients should be made fully aware of the risks and benefits associated with Lemtrada use prior to initiating therapy.

The addition of oral medications in the treatment of MS has had significant clinical impact, especially in a disease state that has historically been dominated by injectable therapies. The availability of oral therapies makes treatment more convenient for the patient but comes at an increased cost overall for the payor. Therefore, as new products gain approval, costs will likely continue to escalate, and health plans will have to closely monitor the clinical and economic impact associated with each new product.

## Clinical and Financial Risks of Not Treating Patients

Although medications and treatment options in the MS landscape are expanding, some patients may choose not to elect for earlier treatment. Early MS may be called a silent disease where inflammation can occur without clinical symptoms. Increase in lesions decreases the plasticity of the brain and results in a gradual development of cognitive impairment, physical impairment, fatigue, and mood fluctuations.[4] Once progression starts presenting symptoms, patients, families, health care providers, and managed care organizations can feel the impact of the disease. Therefore, the goal of disease-modifying treatment is to reduce the early clinical and subclinical disease activity that is thought to contribute to long-term disability.[4] The currently available DMTs have been shown to reduce the occurrence of relapses and slow neurological damage as well as slow disability progression, which can lead to improvement in the patient's quality of life. Irreversible damage means it will be important to target and slow progression.[12]

Even though the cost of treating MS is considerable, the cost of not treating MS is greater. Approximately 70 percent of patients will have a level of disease impairment that will interfere with at least one essential daily task.[13] Further progression may lead to a patient being homebound or further loss of mobility. In addition to the direct costs of medication, there are other clinical and financial costs to MS. Without treatment and prevention of progression, costs of health care can increase from more frequent office visits, devices, and long-term care. The direct and indirect costs associated with MS are currently estimated at $57,000 per patient per year.[13] The total lifetime cost for individuals afflicted with MS

is approximately at $2.2 million, and expected to increase.[13] Early diagnosis of MS is crucial since the treatment differs after the patient progresses into the later stages of MS. Patients who do not receive specialty care are less likely to be on a DMT and are thus increasingly likely to experience more serious levels of disability costing more in the long run. Overall, treating MS can delay disease progression and reduce the risks for further complications, disability, and costs.

## Appropriately Managing the MS Space

In order to appropriately manage the MS space, it is important for payors, clinicians, and patients to work together as a health care team to manage this complex condition. Due to the complexity of the disease, a comprehensive and integrated approach is needed when making the initial diagnosis, continuing to monitor the disease progression, and evaluating response to therapies. Although there are costs associated with treatment, an early diagnosis of MS may prevent the later costs associated with relapse, hospitalizations and long-term care, and indirect costs of lost productivity and disabilities. In order to appropriately manage MS patients, health plans should ensure access to the appropriate product for the right patient. Physicians need to employ careful risk stratification tools prior to initiating treatment, which will lead to more informed clinical decision making.

Due to the lack of best practice guidelines when treating MS, health plans must conduct their own assessments of the available literature and data to inform and develop medical policies. Payors can work with physicians to establish quality metrics to improve outcomes. Even before a treatment plan is started, payors can help improve outcomes by ensuring appropriate access to medications, implementing patient education and support programs, and ensuring physicians adequately understand appropriate use criteria established by the plan. By helping to ensure that patient concerns are considered, this can ultimately reduce inappropriate medication switching and decreased adherence, due to fears of injectable products or side effects.

Payors can help support the modification of the disease course, treating exacerbations, managing symptoms, and promoting continued function though rehabilitation, as well as providing opportunities to ensure emotional support. With comprehensive care, a person's overall health can be better managed, which in turn promotes a healthier patient population.[14] Therefore, particularly in the absence of established consensus treatment guidelines, health plans and providers must collaborate in the development of treatment protocols, including appropriate therapeutic management, monitoring, and patient education and support, as more MS products emerge.

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# Health Care Reform and the Affordable Care Act: Past, Present, and Future

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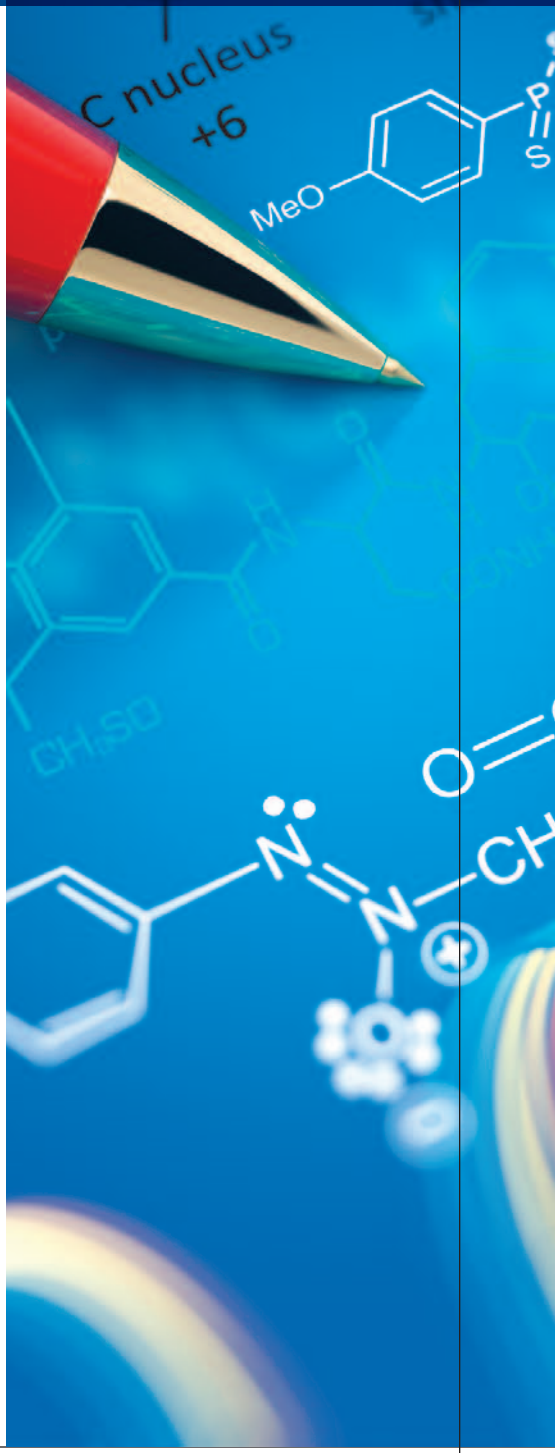



Hard to believe it has been five years since the Affordable Care Act (ACA) was signed into law, and the American health system began a journey down the road of serious health reform.

Since the 2010 Health Care Reform law passed, a lot has happened:

- The Supreme Court has ruled on two ACA-related cases and is set to hear a third in spring 2015;
- Challenges plaguing the rollout of the healthcare.gov website gave late-night comics fodder for months and led to the resignation of Health and Human Services Secretary Kathleen Sibelius;
- More than 10 million Americans gained health insurance on the exchanges or through Medicaid; and
- Hundreds of accountable care organizations (ACOs) were created.

Perhaps the most notable milestone, however, is an analysis that found that in 2013 health care spending grew at a rate of 3.6 percent, the lowest increase since the government began tracking spending in 1960. Some of the low growth is due to the lingering effects of the recession and budget sequestration, while at least part is due to the cost-savings initiatives implemented under the ACA.[1]

Congress may make certain modifications in 2015, however, at the beginning of the year, here is where the ACA stood.

## Individual Insurance Exchanges

The second open enrollment on the exchanges, which ended February 15, 2015, could not have been more different from the first. Unlike the 2014 debacle, the healthcare.gov website successfully handled the deluge of traffic.

Just a month after open enrollment began, 6.4 million Americans — more than 1 million in just the first week — had chosen health insurance plans on the federal exchange (figures were not available for the state exchanges). About a third were new enrollees.

The 2015 health exchange marketplace saw greater competition. More insurers entered the market, which was a major goal of the ACA, and was viewed as a way to help contain costs. Indeed, premium increases for 2015 plans were generally low. However, more plans offered limited, or narrow networks of providers, and increased deductibles, as well as copayments for certain services, including specialty drugs and emergency department visits.[4]

## Legal Challenges

In November 2014, the Supreme Court agreed to hear arguments in King v. Burwell, which challenges the legality of subsidies granted to people who buy health

insurance through the federal marketplace, which operates in 34 states. The case is based on language in the bill that states subsidies would be provided to those who enrolled through an "exchange established by the state."[5]

Nearly 5 million of the 7.1 million newly insured Americans purchased insurance through the federal exchange and about 80 percent of them receive subsidies; therefore, a ruling for the plaintiff may throw millions of Americans back into the land of the uninsured. It could also send the individual insurance marketplace into the so-called "death spiral," with only sick people purchasing health insurance.[5]

## Preventive Services

The ACA required all insurers to provide certain preventive services, including contraceptive care, without cost sharing. Translating the requirement into practice, however, has proven somewhat challenging and led to the second ACA-related case argued before the Supreme Court: Burwell v. Hobby Lobby Stores Inc. In that case, the Court ruled family-owned businesses do not have to offer their employees contraceptive coverage if it conflicts with the owner's religious beliefs.[6]

Implementation of certain preventive services appears to differ depending on the individual plan's policies. For instance:

- Some health plans pay for over-the-counter products (nutritional supplements and certain forms of contraception, including female condoms, the sponge, and emergency contraception), if the patient has a prescription.[7] Others will not cover anything sold over the counter, including any form of contraception.[8]
- Some health plans require patient cost sharing (copayment, deductible) for branded oral contraceptives but not generics, or step therapy before branded drugs are covered.[7,8]
- Some plans require clinical documentation of why women who request NuvaRing® or Ortho Evra® can't use oral contraceptives.[8]
- Some insurers do not cover inpatient facility fees for tubal ligation.[9]
- Some patients are charged for screenings if a medical problem is identified. For instance, Medicare fee-for-service charges patients a 20 percent copayment if a polyp is discovered on a routine colonoscopy.[10] Other plans do not consider a colonoscopy performed after a positive fecal occult blood test, or before age 50 in high-risk individuals, as "screening."[11] Medicare also applies outstanding deductibles to sedation and pathology tests accompanying colonoscopies.[10]

Another surprise to patients comes during wellness or preventive care visits. If they discuss medical problems at these visits, they may find they have to pay out-of-pocket costs.[10]

## Accountable Care Organizations

An April 2014 analysis identified 520 ACOs in the country, 268 of them Medicare Pioneer or Shared Savings ACOs. This represents a 40 percent increase since September 2013. The report also estimated 17 percent of Americans now receive care from an ACO.[12]

In 2013, 23 Pioneer and 220 Shared Savings Medicare ACOs saved more than $417 million for Medicare and earned $460 million in payments.[13]

In late December 2014, the Centers for Medicare & Medicaid Services (CMS) proposed giving Shared Savings ACOs an additional three-year grace period before imposing penalties.[14]

## ACO Quality Measures

Accountable care organizations in the Shared Savings Program have to meet 33 quality measures in four domains: patient/caregiver experience, care coordination/patient safety, preventive health, and at-risk populations.

New measures for 2015 include:

- Avoidable readmissions for patients with multiple chronic conditions, heart failure, and diabetes;
- Depression remission at 12 months after diagnosis;
- All-cause readmission to a skilled nursing facility;
- Documentation of current medications; and
- A new Consumer Assessment of Healthcare Providers and Systems (CAHPS) indicator: Whether the care team discussed prescription drug costs with the patient, called "stewardship of patient resources."[15]

In addition, proposed rules from CMS would encourage more delivery of primary care services from ancillary providers in ACOs, and allow certain non-primary care specialists to participate in multiple ACOs.[15]

## Transparency

A major tenet of health care reform and the ACA is greater transparency around price and quality. Although CMS has been providing such data for hospitals through the Hospital Compare website, it only added data on physician groups and ACOs in late 2014.[16]

In 2016, the agency will begin publicly reporting CAHPS scores for ACOs and group practices of two or more physicians (based on 2015 data). That year, the agency will also publicly report data from the qualified clinical data registry.[17]

## Medicare Part D

In early 2014 CMS issued proposed program changes for Part D plans. Following response, and publication of a final rule in May 2014, CMS issued a final statement on February 6, 2015 (CMS-4159-F2). The final program changes state that the following

modifications that were proposed for Part D in 2014 were not finalized. The program change does not lift protected class designations for Part D drugs, does not require Part D sponsor to include any willing pharmacy, and will not limit the number of Part D plans a plan sponsor may offer.[18]

## Medicaid

By the end of 2014, 28 states (including Washington, D.C.) had expanded Medicaid; seven states were considering it; and 16 states were not planning to expand (See Figure 1).[19] About half of the 12.8 million Americans expected to enroll in Medicaid and the Children's Health Insurance Program (CHIP) by 2016 had actually enrolled. States that expanded enrollment were at 60 percent of projections; those that did not were just at 26 percent. [20]

## Value-Based Reimbursement

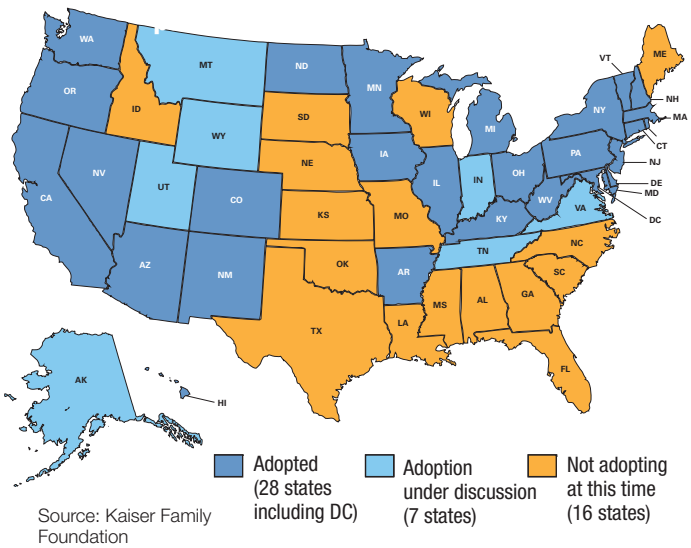
CMS continues to roll out value-based reimbursement in Medicare fee-for-service.

In 2017, all physicians regardless of practice size will be subject to the value-based payment modifier (VBPM), with bonuses and penalties for the year based on their performance in 2015. Penalties also increase for larger physician groups that don't participate in the Physician Quality Reporting System (PQRS) or that deliver low-value (low quality/high cost) care, while bonuses will double for high-achieving providers.[21]

Nonphysician medical professionals such as nurse practitioners and physician assistants come under VBPM in 2018.

The hospital value-based purchasing program now covers an estimated 3,500 hospitals. New diagnosis-related groups for fiscal year 2017 include *Clostridium difficile (C. diff)*, methicillin-resistant *Staphylococcus aureus* (MRSA), and elective delivery prior to 39 weeks completed gestation. For fiscal year 2019, measures will include complication rates for total hip and knee replacements. Data collection for these conditions will begin in 2015 and 2016.[22]

**Figure 1: Current Status of State Medicaid Expansion Decisions[19]**




Source: Kaiser Family Foundation

Penalties for preventable hospital readmissions and hospital-acquired conditions (HACs) continue. In late 2014, CMS announced it was cutting payments by 1 percent to one in seven hospitals, including nearly half of all academic medical centers, because of high rates of HACs. Beginning October 2015, CMS will add rates of surgical-site infections to the list of assessed HACs, and in 2016 rates of *C. diff* and MRSA will join.

In addition, a record 2,610 hospitals were fined in 2014 for high rates of avoidable 30-day readmissions.[23] This is due, in part, to the two new conditions CMS added to the list of readmissions assessed: chronic obstructive pulmonary disease and knee and hip replacements. They join myocardial infarction, heart failure, and pneumonia. The good news is readmission rates are dropping; down to 18 percent in 2013 from nearly 20 percent in 2010.[24]

On the commercial side, Catalyst for Payment Reform estimates that in 2014 about 40 percent of commercial health plan reimbursements were tied to quality or cost, including 38 percent of all hospital payments; 10 percent of all outpatient specialist payments; and 24 percent of all outpatient PCP payments. That compares to just 11 percent in 2013. Payment models include shared savings, shared risk, and pay for performance.[25]

Employers are also pushing value-based reimbursement, contracting directly with centers of excellence to provide services such as cardiovascular care and joint replacement for a bundled payment. For instance, GE announced in November 2014 that it was contracting with four centers of excellence around the country to provide joint replacements for its employees and retirees. The company already has similar arrangements for organ transplants, bariatric surgeries, and certain types of cancer care.[26]

## Medicare Advantage

Concerns that Medicare Advantage (MA) cuts would lead to a mass exodus of plans have proved unfounded. Since 2012, payments to Medicare Advantage Plans dropped from 114 percent of fee-for-service rates to 106 percent with no change in accessibility, while average premiums have dropped 10 percent. Meanwhile, enrollment has grown by a third and plan profitability and profit margins have remained high.[27] However, the administration canceled the planned 2015 cuts to Medicare Advantage Plans.

In 2015, the Kaiser Family Foundation reports 99 percent of beneficiaries (100 percent in urban areas) will have access to Medicare Advantage Plans. They will be able to choose from the same number of plans, on average, as the previous year, and 95 percent will be able to remain in the same plan.[28]

This year about 78 percent of beneficiaries will have access to no-premium plans. Plans that require premiums have increased the premium an average of 20 percent. Payors are limiting benefits and networks in no-premium plans, however, in an effort to control costs. [28]

## Postponements

The Obama administration has postponed implementing several components of the ACA, including:[29]

- Small-employer health option program. Federal exchanges offering health plans for small businesses won't open until some time this year.
- Basic Health Program. This program would have provided even more affordable health insurance than the bronze plan on the exchanges for low-income people who don't qualify for Medicaid. Its implementation was delayed until later in 2015.
- Employer mandate. The requirement that employers with 50 or more full-time equivalent employees provide affordable health insurance to their employees or risk paying penalties has not been fully implemented. Companies with 51 to 99 employees have until 2016 to provide coverage; while those with 100 or more employees must offer coverage to 70 percent of their full-time employees in 2015 and 95 percent in 2016 and beyond.

## Equal Employer Coverage

The requirement, which was supposed to become effective in 2010, that employers who are not self-insured cannot offer better health plans to executives than their employees remains in limbo as the IRS struggles to develop regulations.

The Affordable Care Act was the most comprehensive, complex health care–related legislation passed since Medicare was established in 1965. The bumps and potholes related to its rollout were to be expected, as were ongoing legislative changes to the law.

It remains to be seen what, if anything, will change in 2015 — including, potentially, the repeal of the law.

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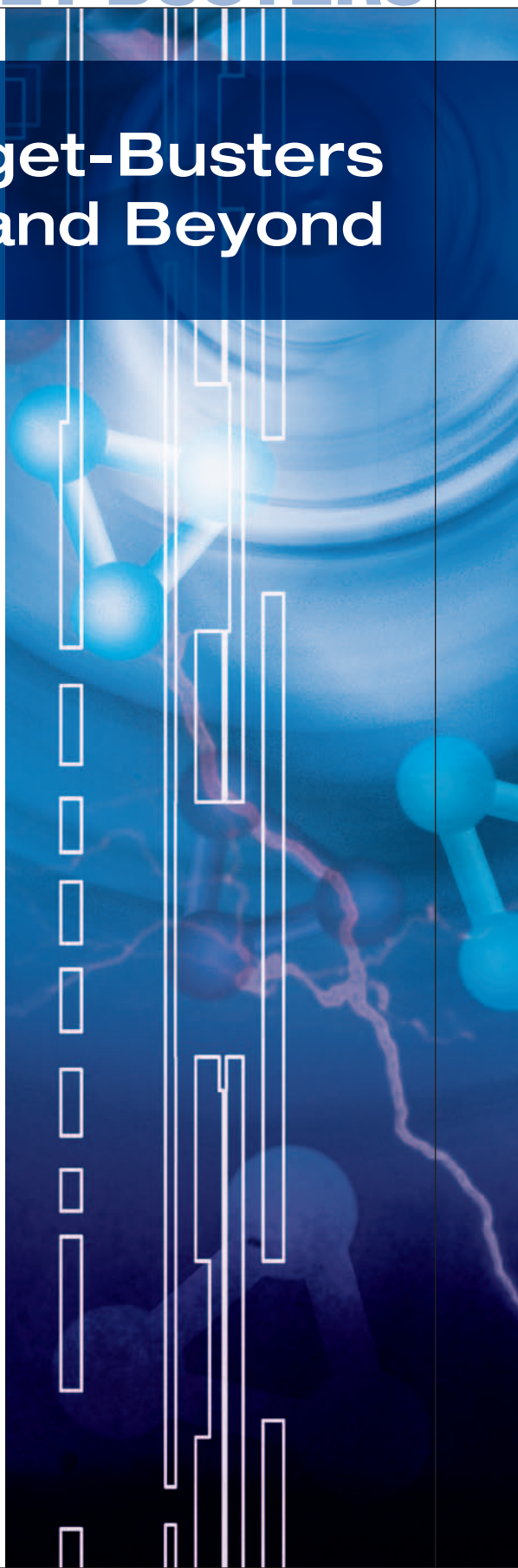
# Potential Budget-Busters for 2015 and Beyond



Utilization of several therapies that were either recently approved or are pending approval in 2015 are expected to have a significant impact on drug spending. Of course, products used to treat hepatitis C virus and other specialty conditions will remain major cost drivers. However, there are a few new categories to keep on the radar screen for the upcoming years.

## Hypercholesterolemia

The first group of products to keep an eye on is the PCSK9 inhibitors. These products are expected to hit the market in the third quarter of 2015 (See Table 1). These injectable drugs target the PCSK9 protein. The protein, when present, decreases the liver's ability to clear LDL-C from the blood. The PCSK9 inhibitors work by blocking the PCSK9 protein, allowing cholesterol metabolism to occur and resulting in reduced LDL-C levels.

It is anticipated that the PCSK9 inhibitors will be approved for patients intolerant of or unresponsive to statin therapy. Analysts project PCSK9 inhibitors could cost as much as $1,000 per month and may be indicated for over 10 million patients not well controlled with statins. This would create a market that could reach $10 billion annually.[1] Amgen filed for FDA approval of evolocumab (AMG 145) in August 2014, with an anticipated Prescription Drug User Fee Act (PDUFA) target action date of August 27, 2015. The approval of evolocumab may be preceded by another PCSK9 inhibitor. Sanofi and Regeneron have reported favorable results from phase 3 trials of alirocumab, which will undergo an expedited review by the FDA by July 24, 2015, which is six months from the date of its FDA submission. Next, Pfizer's bococizumab (RN316) is expected to be submitted for FDA review in 2016. FDA labeling, national cholesterol treatment guidelines, and health plan policies will be significant factors influencing the uptake of these therapies.

Another class of medications developed to treat hypercholesterolemia includes the cholesteryl ester transfer protein (CETP) inhibitors. These agents work by inhibiting CETP, increasing HDL or "good cholesterol" levels and decreasing LDL-C levels. Merck's anacetrapib and Eli Lilly's evacetrapib are two investigational agents in this class. While the status of these drugs remains undefined, it is worth noting that a study published in the November 2014 issue of the *New England Journal of Medicine* suggests HDL levels may not be closely correlated with cardiovascular outcomes, and that cholesterol efflux capacity is more significantly linked to the development of cardiovascular disease.[2] Currently, the role of CETP inhibitors in treating hypercholesterolemia remains undefined.[3]

**Table 1 PCSK9 Inhibitors**

| PCSK9 Inhibitors with Expected FDA Approval in 2015 | Anticipated FDA Indications for Use |
|---|---|
| Alirocumab | Heterozygous familial hypercholesterolemia and hypercholesterolemia in patients intolerant or nonresponsive to statin therapy |
| Evolocumab | Above indications with additional homozygous familial hypercholesterolemia indication |

**Table 2 New Oncology Agents**

| Oncology Agents | Indications for Use |
|---|---|
| **PD-1 Inhibitors** | |
| Pembrolizumab (Keytruda — approved September 2014) | Advanced or unresectable melanoma in patients no longer responding to other therapies |
| Nivolumab (Opdivo — approved December 2014) | Unresectable or metastatic melanoma and disease progression following ipilimumab (Yervoy) and, if BRAF V600 mutation positive, also a BRAF inhibitor |
| **Selective Inhibitor of Cyclin-Dependent Kinases (CDK) 4 and 6** | |
| palbociclib (Ibrance — PDUFA goal date for FDA decision: April 13, 2015) | First-line treatment for patients with estrogen receptor positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer |

**Table 3 Immunotherapy Agents**

| Interleukin-17A (IL-17A) Blockers for Treatment of Plaque Psoriasis | Status |
|---|---|
| Secukinumab (Cosentyx) — Novartis | Obtained FDA approval, January 2015 |
| Brodalumab — Amgen and AstraZeneca | Phase 3 trials |
| Ixekizumab — Eli Lilly | Phase 3 trials |
| MK-3222 — Merck | Trials under way |
| Guselkumab — Johnson & Johnson | Trials under way |

## Oncology

Development of therapies on the oncology front continues, driving innovation and with the potential to have a significant impact on health care costs (See Table 2). In 2014, two medications from a new class of therapies, programmed death receptor-1 (PD-1) blocking antibodies, obtained FDA approval for the treatment of melanoma. Merck's pembrolizumab (Keytruda®) was approved in September for treatment of advanced or unresectable melanoma in patients no longer responding to other drugs. Then, in December, Bristol-Myers Squibb's nivolumab (Opdivo®) obtained accelerated FDA approval for the treatment of unresectable or metastatic melanoma and disease progression in patients previously treated with ipilimumab (Yervoy®) and, if BRAF V600 mutation positive, a BRAF inhibitor. Keytruda and Opdivo are both intravenously administered with weight-based dosing; therefore, the cost of these products is variable. However, for a theoretical 70 kg patient, both products have a monthly cost of over $10,000.

Other PD-1 blocking antibodies are in development. These therapeutic agents are being studied for use in the treatment of a wide variety of tumor types, including NSCLC, ovarian, and gastric tumors. It is reasonable to anticipate the PD-1 inhibitors will play a growing role in the oncology space following the approval of additional products and various indications.

Another oncology drug likely to be approved in 2015 is Pfizer's palbociclib (Ibrance). In October 2014, the FDA announced the drug will receive priority review as a first-line treatment for patients with estrogen receptor positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer. One key trial showed that when taken with letrozole, palbociclib was able to delay tumors from growing for a median of more than 20 months, about twice as long as current treatment alone. The PDUFA date for a decision is April 13, 2015.[4]

## Immunotherapy

Additionally, breakthrough immunotherapies for treatment of plaque psoriasis are expected to drive drug spend in 2015. The condition affects an estimated 6.7 million adults in the United States.[5] These new agents, which work by blocking interleukin-17A (IL-17A), a protein found in high concentrations in skin affected by psoriasis, are in various stages of clinical development or FDA review (See Table 3). The first drug approved by the FDA was secukinumab (Cosentyx™). It earned an endorsement for approval by the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee in October 2014 and obtained FDA approval in early 2015.[6] This Novartis drug is the first IL-17A inhibitor approved to treat moderate-to-severe plaque psoriasis. Phase 3 studies demonstrated that over 70 percent of patients treated with secukinumab achieved clear skin or almost clear skin, after 16 weeks of treatment. Amgen and AstraZeneca are codeveloping another IL-17A inhibitor, brodalumab. Phase 3 study data released in late 2014 indicate that both secukinumab and brodalumab, each in separate trials, demonstrated superiority in clearing skin blemishes in the treatment of psoriasis over ustekinumab (Stelara®).[7,8] Eli Lilly is also developing an IL-17A inhibitor, ixekizumab, which is in phase 3 studies, while Merck's MK-3222 and Johnson & Johnson's guselkumab are in development as well. Given the large patient population and perceived need for therapeutic alternatives, expectations are that demand for the new IL-17A inhibitors will be significant. Projections are that sales of Cosentyx alone will range from $700 million to a billion dollars annually by 2020,[9] an indication that demand for these drugs may result in management challenges and significant costs.

## Cystic Fibrosis

Lastly, drugs new to the market, and some that are still under development, are expected to change the landscape of cystic fibrosis treatment. Ivacaftor (Kalydeco®), developed by Vertex, was approved in 2012 for use in cystic fibrosis patients ages 6 years and older with G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[10] Ivacaftor, the first CFTR potentiator to market, is notable for its $300,000 cost per year for each patient. Vertex is awaiting FDA approval for a combination product, ivacaftor with another CFTR potentiator, VX-809 (lumacaftor). This combination product was submitted for FDA review in November for patients ages 12 years and older, with two copies of the F508del mutation. This is significant because ivacaftor alone is not effective in cystic fibrosis patients homozygous for the F508del mutation in the CFTR gene, a population comprising the majority of cystic fibrosis patients. It is estimated that there are about 30,000 people in the United States with cystic fibrosis and about half of these have two faulty copies of the F508del gene.[11] If approved, VX-809 is expected to be in the same price range as Kalydeco, but with the potential to treat a far greater number of cystic fibrosis patients, poised to become a managed care budget-buster.[12]

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# Specialty Outlier Analysis:
## Identifying Cost-Saving Interventions in Outlier Patient Populations

The Specialty Outlier Program is a comprehensive clinical program that reviews the health plan population to identify specific areas in which clinical interventions and policy changes may be introduced to promote best practices and reduce costs to both patient and plan, while maintaining an equivalent or improved standard of care. Health plan data is used to identify specific members with high-spend disease states (See Table 1) whose costs are substantially greater than other members with the same disease state.

By utilizing data from medical and prescription claims, prior authorizations and medical records (when available), the Magellan Rx Management clinical team is able to pinpoint trends that may contribute to unnecessarily high costs of care. Within the Specialty Outlier Program, a patient's outlier status is determined by total patient spend significantly exceeding the average member with the same disease state (usually a >2.5 standard deviation benchmark). In a pilot program conducted within a 2.8 million member regional health plan, a number of trends were identified within the outlier population allowing interventions to improve patient care and reduce health plan costs.

The most significant contributor to unnecessarily high cost was the site of service (SOS) or the physical location where treatment was administered. A member receiving Remicade® (infliximab) infusions for treatment of rheumatoid arthritis (RA) serves as a fitting case study. Of the 958 fully insured members evaluated, the average total spend per member being treated for RA was $17,829. For the purposes of the pilot, member cases with total spend exceeding $64,000 were evaluated. Total spend within the outlier population ranged from $64,074 to $233,394, with an average total spend of $127,971. Investigation revealed that most of these outlier members had been referred by their physician to a hospital outpatient setting, rather than receiving their infusion services at their physician's office or at

**Table 1 — Examples of Chronic Disease States Associated with High Annual Costs of Therapy**

| | |
|---|---|
| Multiple Sclerosis (MS) | Rheumatoid Arthritis (RA) |
| Crohn's Disease (CD) | Colon Cancer |
| Cystic Fibrosis (CF) | Psoriasis/Psoriatic Arthritis |
| Prostate Cancer | Hereditary Angioedema (HAE) |

**Table 2 Cost Per Unit of Remicade for "Typical RA Patient" Based on Site of Administration**

| Hospital Outpatient Clinic | Physician's Office | Difference |
|---|---|---|
| Average cost per unit: $230 | Average cost per unit: $71 | Cost per unit (difference): $159 |
| Cost per claim<br>average of 50 units = $11,500 | Cost per claim<br>average of 50 units = $3,550 | Cost per claim (difference): $7,950 |
| Cost/6 claims/year = $69,000 | Cost/6 claims/year = $21,300 | Cost per year<br>(difference): $47,700 |
| Patient out of pocket (20%) =<br>$2,300 per visit<br>$13,800 per year | Patient out of pocket (20%) =<br>$710 per visit<br>$4,260 per year | Patient out of pocket<br>(difference):<br>$1,590 per visit<br>$9,540 per year |

another cost-effective treatment site (i.e., free-standing infusion clinic or home care). This had significant financial implications (See Table 2).

As a comparison, the average cost per unit of Remicade at a hospital outpatient clinic is $230 versus $71 per unit at a physician's office. Extrapolating this price difference across the average number of units per claim (50) and the average number of claims each year (6) reveals an additional average cost of $47,700 per member per year when the member receives infusions at a hospital outpatient facility. In a hypothetical average patient receiving 50 units per claim with a 20 percent coinsurance, the out-of-pocket cost of each hospital visit would be $2,300 (after their deductible has been met), compared to $710 at a physician office setting — a difference of $1,590 per infusion. Across six infusions, this would represent up to $9,540 of out-of-pocket savings for plan members. There are a range of reasons that patients or prescribers may opt for the use of a hospital outpatient infusion site, but given the substantial difference in cost, an SOS program has the potential to result in significant savings for members and plans alike.

Another common occurrence among outlier patient cases was the use of costly medications in place of a cheaper alternative. In some cases, expensive drugs may be prescribed because contracts and rebate agreements make the use of these agents financially beneficial to providers. While these drugs may not necessarily be clinically inappropriate, they may, in some instances, offer no clinical advantage over the lower-cost preferred alternative. Analysis of pharmacy and medical claims data can help identify areas of opportunity for potential reimbursement contract restructuring to ensure members are receiving medications that are both clinically appropriate and cost-efficient. Additionally, more expensive medications may be prescribed due to a simple therapeutic oversight. The Specialty Outlier pilot program identified several instances in which Fusilev® was being prescribed in place of generic leucovorin. Fusilev (levoleucovorin), the active enantiomer in leucovorin, is a brand-name medication that costs approximately 60 times more than leucovorin, which is available as a generic. The two medications are therapeutically equivalent, but due to drug shortages of generic leucovorin, many facilities switched patients to Fusilev as an alternative. At the time the pilot program was conducted there was no such shortage; however, many of the members in the outlier patient population for high-cost disease states (e.g., prostate cancer) were still receiving Fusilev. By analyzing pharmacy and medical claims data, Magellan Rx Management is able to identify such oversights and help health plans reduce costs for both the plan and the member.

In addition to actively analyzing the current outlier population for a health plan, Magellan Rx Management provides health plans with insight regarding proactive reviews of policies to identify areas of improvement. The trends identified within the outlier population support health plans' efforts to audit policies and procedures such as use of VEGF in members with colon cancer and strengthening of biologic DMARD policies to require a proper trial of oral DMARDs as first-line therapy for RA. These interventions, as well as several others identified in the pilot, can provide valuable support for plans by helping to reduce the cost of health care for high-cost members within the population, as well as by helping to prevent future mismanagement.

# Biosimilar Update: FDA Guidance, Accepted Applications, and Remaining Challenges

In 2013, the FDA released four draft guidance documents detailing biosimilar regulations: quality guidelines, scientific guidelines, questions and answers pertaining to the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), and rules on biosimilar sponsor interactions with FDA regulators.[1] However, several unanswered questions regarding the biosimilar approval process remain. To address these questions, the FDA is continuing to release draft guidance documents, two of which were released in 2014.

On May 13, 2014, the FDA released an updated draft guidance titled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," which specifically addresses the type and amount of data the FDA will require in order to substantiate biosimilarity. The draft guidance delineates the elaborate process that a sponsor would need to follow in order to demonstrate that the biological product is biosimilar to its reference product.[2] The guidance outlines the pharmacokinetic (PK) and pharmacodynamic (PD) data required to support biosimilarity between the biological product and the reference product.[2] "The guidance discusses some of the overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials."[2] However, how the FDA will administer the BPCI Act remains a work in progress as this is one in a series of guidelines the FDA is developing.[2]

The draft guidance describes "three key elements" that are significant as part of the FDA's assessment of the development of biosimilar products.[2] These elements include:

1. Exposure and response assessment
2. Evaluation of residual uncertainty
3. Assumptions about analytical quality and similarity

The draft discusses four different assessment categories, and that "the result of the comparative analytical characterization may lead to one of the four assessments within a development-phase continuum."[2]

## Biosimilar Categories

The categories are as follows:

**Highly similar with fingerprint-like similarity:** A submission is considered practically identical to its reference product, "based on integrated, multi-parameter approaches."[2] These drugs would require "targeted and

**Table 1 Status of Biosimilar Applications Submitted to the FDA[8,9]**

| Biologic | Biosimilar Manufacturer | Reference Product | Date Application Submitted | U.S. Annual Spend of Reference Product |
|---|---|---|---|---|
| EP2006 (Zarzio®) | Novartis | Neupogen® | July 2014 | $1.2 billion |
| BOW015 (Remsima™) | Celltrion Inc. | Remicade® | August 2014 | $3 billion |
| pegfilgrastim | Apotex | Neulasta® | December 2014 | $3.5 billion |
| Retacrit™ | Hospira | Epogen® | December 2014 | $3.4 billion |

selective" further study to alleviate residual uncertainty and demonstrate their biosimilarity.[2]

**Highly similar:** "The proposed biosimilar product meets the statutory standard for analytical similarity. The results of the comparative analytical characterization permit high confidence in the analytical similarity of the proposed biosimilar and the reference product, and it would be appropriate for the sponsor to conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity."[2]

**Similar:** "Further information is needed to determine whether the product is highly similar to the reference product. Additional analytical data or other studies are necessary to determine whether observed differences are within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product."[2]

**Not similar:** This tier applies to products that do not measure up to their references nor meet the standards to determine analytical similarity.[2]

## FDA Guidance

On August 4, 2014, the FDA released a draft guidance titled, "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act," which concentrates on the type of information that reference product sponsors are encouraged to provide in order to assist in the FDA's determination of the date of first licensure for products.[6] Specifically under 351(k)(7), a biosimilar application cannot be submitted until four years after the date of the reference product's first licensure, and subsequently, the FDA cannot approve it until 12 years after the date the reference product was first referred to in the biosimilar application approval pathway.[6]

The reference product exclusivity period is defined as the period of time the product cannot be licensed or submitted for review.[6] Ultimately, the decision made under the approval pathway pertaining to the date of first licensure of a reference product is a decision on eligibility for the reference product exclusivity, and when exclusivity shall begin.[6]

The Draft Exclusivity Guidance provides a list of information the sponsor should submit in order to show that the sponsor meets the requirements to qualify for the exclusivity set forth in the biosimilar application approval pathway.[6] This includes:

1. List of all licensed biological products that are structurally related to the biological product that is subject to the 351(a) application being considered.
2. List of those for which the sponsor or one of its affiliates, including any licensors, predecessors in interest, or related entities, are the current or previous license holder of the biological products listed above.
3. Description of structural differences between those products and the Biologics License Application (BLA) product under consideration.
4. Evidence of the change in safety, purity, and/or potency between those products and the BLA product under consideration.

## Biosimilar Products Reference

On September 9, 2014, the FDA published the first edition of the *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity Evaluations.*[7] The *Purple Book* is essentially the equivalent of the pharmaceutical *Orange Book*, and seeks to assist regulatory agents, generic manufacturers, and physicians by providing them with information pertaining to biological products, including any biosimilar and interchangeable products.[7] Although the publication of the *Purple Book* comes several years after the BPCI Act, this represents a significant step in the right direction toward the identification of biological products.

The *Purple Book* is divided into two sections: The first part lists the products the Center for Drug Evaluation and Research (CDER) has approved, and the second part

**Table 2 Top Biologics, When Exclusivity Period Ends, and When BLAs Can Be Submitted[10]**

| Active Pharmaceutical Ingredient (API) | Brand Name | FDA Did Not Accept Biosimilar Applications Before: | FDA Will Not Approve Biosimilar Applications Before: |
|---|---|---|---|
| Adalimumab | Humira® | 12/31/2006 | 12/31/2014 |
| Bevacizumab | Avastin® | 02/26/2008 | 02/26/2016 |
| Canakinumab | Ilaris™ | 06/17/2013 | 06/17/2021 |
| Cetuximab | Erbitux® | 02/12/2008 | 02/12/2016 |
| Darbepoetin Alfa | Aranesp® | 09/17/2005 | 09/17/2013 |
| Eculizumab | Soliris® | 03/16/2011 | 03/16/2019 |
| Epoetin Alfa | Eprex® | 02/25/2003 | 02/25/2011 |
| Etanercept | Enbrel® | 11/02/2002 | 11/02/2010 |
| Infliximab | Remicade® | 08/24/2002 | 08/24/2010 |
| Natalizumab | Tysabri® | 11/23/2008 | 11/23/2016 |
| Palivizumab | Synagis® | 06/19/2002 | 06/19/2010 |
| Pegfilgrastim | Neulasta® | 01/31/2006 | 01/31/2014 |
| Ranibizumab | Lucentis® | 06/30/2010 | 06/30/2018 |
| Rituximab | Rituxan® | 11/26/2001 | 11/26/2009 |
| Trastuzumab | Herceptin® | 09/25/2002 | 09/25/2010 |
| Ustekinumab | Stelara® | 09/25/2013 | 09/25/2021 |

lists the products the Center for Biologics Evaluation and Research (CBER) has approved.[7] The *Purple Book* will include the following information:

- The date a biological product was licensed under section 351(a) of the Public Health Service Act (PHSA);
- Whether the FDA evaluated the biological product for reference product exclusivity under 351(k)(7) of the PHSA; and
- Whether the FDA has determined a biological product is biosimilar or interchangeable with a reference biological product.[7]

Therefore, as the biosimilar market grows with the emergence of new products and exclusivity is granted, the *Purple Book* will be updated over time to reflect these changes.

## First Approved Biosimilar

In July 2014, Sandoz, a Novartis subsidiary, announced the FDA had accepted its Biologics License Application for filgrastim using the biosimilar application approval pathway.[4] The reference product, Neupogen® (Amgen Inc.), is indicated "to decrease rates of infection in patients with nonmyeloid malignancies who are already receiving chemotherapy."[4]

"This filing acceptance represents a significant step toward making high-quality biologics more accessible in the U.S. and we applaud FDA for its progress in making this a reality," said Mark McCamish, MD, PhD, head of Global Biopharmaceutical & Oncology Injectables Development at Sandoz. "As they've done in Europe and other highly-regulated markets around the world, biosimilars are poised to increase U.S. patient access to affordable, high-quality biologics, while reducing the financial burden on payers and the overall healthcare system."[4]

If approved, Sandoz's biosimilar will likely be marketed under the brand name Zarzio®, which has been marketed in more than 40 countries outside of the United States with approximately 6 million patient-exposure days worth of data.[4] Sandoz now has six biosimilar molecules in phase 3 clinical trials/filing preparation, more than any other drug manufacturer, making Sandoz the pioneer and global leader in the biosimilars market.[4]

Also, if approved, this may offer insight into how manufacturers may approach the pricing of their products relative to reference products.[5] After the passage of the BPCI Act, stakeholders indicated, "they believed biosimilar drugs could save consumers and the federal government billions each year by incentivizing market competition."[5] However, due to the challenges drug

manufacturers are facing bringing biosimilars to the market, some have expressed concerns that the true savings could be much lower than originally anticipated.[6]

## Challenges Still Remain

The new guidance did not address how the biological product could be interchanged with the reference product. The FDA has established a complex process for the biosimilar to establish interchangeability with the reference product. The FDA did provide some guidance as to what drug manufacturers need to do in order to submit biosimilar drugs for FDA review, but details of the process are still undefined. The most substantial challenges still remain with defining parameters for indications, substitution, and physician and patient uptake.

A major area of consideration is the determination of approved indications for biosimilar agents. This may be complex as there may not be clinical evidence submitted to support each clinical indication. Applying safety and efficacy data across all indications can pose difficulties, and may be inappropriate in the absence of strong scientific data or variation in the data and how it pertains to the different therapeutic indications. This may impact the ability to optimize the savings potential associated with biosimilar products.

Substitution remains an issue because there is still ambiguity surrounding whether pharmacists will be allowed to substitute a biosimilar for a biologic without physician approval. The Patient Protection and Affordable Care Act allows interchangeable biosimilars to be substituted for the reference product without health care provider approval, but it is up to each state to determine how it will allow such substitutions.

Additionally, the FDA has stated, "It would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment."[3] Therefore, automatic substitution by pharmacists might eventually be an irrelevant conversation.

Naming of the biosimilar agent is another potentially controversial area. There are two schools of thought on this. Many branded biologic entities feel there should be distinctive generic names for the drugs, and contend that using the same names for different medicines could cause more confusion and ultimately make pharmacovigilance more difficult.[5] Biosimilar companies feel that the naming issue could cause confusion among patients, leading patients to think that the drug is not as safe or effective as the original.[5]

Manufacturers of biosimilars in the United States must overcome the challenge of educating providers regarding biosimilars, developing strategies to ease physicians' concerns, and overcoming reluctance to utilize the new products. Biosimilars will have to be marketed similarly to branded agents, which may also impact the overall cost-savings potential associated with these products.

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# PIPELINE TRENDS

| NEW DRUG APPROVALS | | | |
|---|---|---|---|
| **Drug** | **Manufacturer** | **Approval Date** | **Indication** |
| Lemtrada™ (alemtuzumab) injection | Genzyme | November 14, 2014 | CD52-directed cytolytic monoclonal antibody for the treatment of relapsing forms of multiple sclerosis |
| Hysingla™ ER (hydrocodone) tablet | Purdue | November 20, 2014 | Extended-release opioid analgesic for around-the-clock management of moderate to severe chronic pain |
| Blincyto™ (blinatumomab) injection | Amgen | December 3, 2014 | Bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome–negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia |
| Signifor® LAR (pasireotide) injection | Novartis | December 15, 2014 | Long-acting somatostatin analog formulation for treatment of patients with acromegaly |
| Viekira Pak™ (ombitasvir/paritaprevir/ritonavir with dasabuvir) tablet | AbbVie | December 19, 2014 | NS5A inhibitor, NS3/4A protease inhibitor and CYP3A inhibitor combination co-packaged with a non-nucleoside NS5B palm polymerase inhibitor for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection |
| Lynparza™ (olaparib) capsule | AstraZeneca | December 19, 2014 | First-in-class oral poly (ADP-ribose) polymerase (PARP) inhibitor for the treatment of advanced ovarian cancer |
| Zerbaxa™ (ceftolozane/ tazobactam) injection | Cubist Pharmaceuticals | December 19, 2014 | Cephalosporin and beta-lactamase inhibitor for the treatment of complicated intra-abdominal infections and complicated urinary tract infections |
| Rapivab™ (peramivir) injection | BioCryst Pharmaceuticals | December 19, 2014 | Influenza virus neuraminidase inhibitor for the treatment of acute uncomplicated influenza in adults |
| Opdivo® (nivolumab) injection | Bristol-Myers Squibb | December 22, 2014 | Programmed death receptor-1 (PD-1) blocking antibody for the treatment of advanced melanoma |
| Saxenda® (liraglutide) injection | Novo Nordisk | December 23, 2014 | Once-daily glucagon-like peptide-1 (GLP-1) analogue for the treatment of obesity |
| Namzaric™ (donepezil/ memantine) capsule | Actavis/Adams | December 23, 2014 | NMDA receptor antagonist and acetylcholinesterase inhibitor fixed-dose combination for the treatment of moderate to severe Alzheimer's disease |
| Rytary™ (carbidopa/levodopa) capsule | Impax Laboratories | January 7, 2015 | Extended release aromatic amino acid decarboxylation inhibitor and aromatic amino acid combination indicated for the treatment of Parkinson's disease |
| Savaysa™ (edoxaban) tablet | Daiichi Sankyo Company | January 8, 2015 | Once daily factor Xa inhibitor anticoagulant indicated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for treatment of DVT and PE |
| Duopa™ (carbidopa/levodopa) enteral suspension | AbbVie | January 12, 2015 | Aromatic amino acid decarboxylation inhibitor and aromatic amino acid combination formulated as an enteral suspension for the treatment of motor fluctuations in patients with advanced Parkinson's disease |
| Prestalia® (amlodipine besylate/perindopril arginine) tablet | Symplmed | January 21, 2015 | CCB and long-acting ACE inhibitor combination for the treatment of hypertension |
| Cosentyx™ (secukinumab) injection | Novartis | January 21, 2015 | Selective interleukin-17A inhibitor for the treatment of moderate to severe plaque psoriasis |
| Natpara® (parathyroid hormone) injection | NPS Pharmaceuticals | January 23, 2015 | Recombinant human parathyroid hormone 1-84 indicated to control hypocalcaemia in patients with hypoparathyroidism |
| Evotaz™ (atazanavir/cobicistat) tablet | Bristol-Myers Squibb | January 29, 2015 | Once daily fixed dose combination of protease inhibitor and a pharmacokinetic enhancer for the treatment of HIV-1 infection |
| Prezcobix™ (darunavir/cobicistat) tablet | Janssen | January 29, 2015 | Once daily fixed dose combination of protease inhibitor and a pharmacokinetic enhancer for the treatment of HIV-1 infection |
| Glyxambi® (empagliflozin/linagliptin) tablet | Boehringer Ingelheim Pharmaceuticals | January 30, 2015 | Sodium glucose co-transporter-2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DDP-4) inhibitor combination for the treatment of adults with type 2 diabetes |
| Ibrance® (palbociclib) capsule | Pfizer Inc | February 3, 2015 | Cyclin-dependent kinase 4/6 (CDK4/6) inhibitor for the combination treatment of ER+, HER2- metastatic breast cancer |
| Lenvima™ (lenvatinib) capsule | Eisai Inc | February 13, 2015 | Oral multiple receptor tyrosine kinase (RTK) inhibitor for the treatment of progressive radioiodine-refractory differentiated thyroid cancer |

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

| NEW FDA-APPROVED INDICATIONS | | |
|---|---|---|
| **Drug** | **Approval Date** | **Indication** |
| Olysio™ (simeprevir) | November 5, 2014 | Approved for use in combination with sofosbuvir for genotype 1 patients with chronic hepatitis C |
| Cyramza® (ramucirumab) | November 5, 2014 | Approved in combination with paclitaxel for advanced gastric cancer after prior chemotherapy |
| Invega® Sustenna® (paliperidone) | November 13, 2014 | Approved for schizoaffective disorder |
| Avastin® (bevacizumab) | November 14, 2014 | Approved in combination with chemotherapy for platinum-resistant recurrent ovarian cancer |
| Jakafi® (ruxolitinib) | December 4, 2014 | Approved for treatment of patients with polycythemia vera |
| Xgeva® (denosumab) | December 5, 2014 | Approved for hypercalcemia of malignancy refractory to bisphosphonate therapy |
| Cyramza® (ramucirumab) | December 12, 2014 | Expanded approval to treat aggressive non-small cell lung cancer |
| Somatuline® Depot (lanreotide acetate) | December 16, 2014 | Approved to treat gastroenteropancreatic neuroendocrine tumors |
| Kalydeco® (ivacaftor) | December 29, 2014 | Approved for use in patients with cystic fibrosis ages 6 and older who have the R117H mutation |
| Imbruvica® (ibrutinib) | January 29, 2015 | Approved for use in Walfenstrom's Macroglobulinemia |
| Vyvanse® (lisdexamfetamine dismesylate) | January 30, 2015 | Approved to treat binge-eating disorder |
| Lucentis® (ranibizumab) | February 6, 2015 | Approved to treat diabetic retinopathy |
| Banzel® (rufinamide) | February 12, 2015 | Expanded approval as an adjunctive treatment of seizures in pediatric patients now 1 year and older (previously 4 years and older) |
| Revlimid® (lenalidomide) | February 17, 2015 | Expanded approval for use in combination with dexamethasone to include patients newly diagnosed with multiple myeloma |

| NEW FORMULATIONS AND DOSAGE FORMS | | |
|---|---|---|
| **Drug** | **Approval Date** | **Advertised Advantage** |
| Uceris® (budesonide) | October 8, 2014 | Rectal foam for the induction of remission in patients with mild to moderate ulcerative colitis |
| Zubsolv® (buprenorphine/naloxone) | December 11, 2014 | Two higher dosage strengths (8.6 mg/2.1 mg and 11.4 mg/2.9 mg) approved |
| Granix™ (tbo-filgrastim) | December 19, 2014 | Approved for self-administration |
| Erwinaze® (asparaginase Erwinia chrysanthemi) | December 19, 2014 | Approved for intravenous administration |
| Qnasl® (beclomethasone dipropionate) | December 17, 2014 | 40mcg approved for treatment of nasal symptoms associated with allergic rhinitis in children 4–11 |
| Zohydro ER® (hydrocodone ER) | January 30, 2015 | Approved for new abuse-deterrent formulation that does not change the release properties using BeadTek technology |

| NEW FIRST-TIME GENERIC DRUG APPROVALS | | |
|---|---|---|
| **Generic Product** | **Reference Drug** | **Approval Date** |
| Olopatadine | Patanase® nasal spray | October 8, 2014 |
| Ivermectin | Stromectol® tablet | October 24, 2014 |
| Valganciclovir | Valcyte® tablet | November 4, 2014 |
| Bimatoprost | Latisse® ophthalmic solution | December 1, 2014 |
| Estradiol | Vivelle-Dot® transdermal patch | December 19, 2014 |
| Desvenlafaxine | Pristiq® tablet | December 31, 2014 |
| Ritonavir | Norvir® tablet | January 15, 2015 |
| Esomeprazole | Nexium® capsule | January 26, 2015 |

**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. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and prandial insulin has not been studied.

**CONTRAINDICATIONS:** Do not use 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). Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

**WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors:** Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. 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. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One 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. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-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: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

**ADVERSE REACTIONS: Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

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

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

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

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

| | | | |
|---|---|---|---|
| Constipation | 5.3 | 0.9 | 1.7 |
| Dyspepsia | 5.2 | 0.9 | 2.6 |
| **Add-on to Metformin + Glimepiride** | | | |
| | Victoza® 1.8 + Metformin + Glimepiride N = 230 | Placebo + Metformin + Glimepiride N = 114 | Glargine + Metformin + Glimepiride N = 232 |
| **Adverse Reaction** | (%) | (%) | (%) |
| Nausea | 13.9 | 3.5 | 1.3 |
| Diarrhea | 10.0 | 5.3 | 1.3 |
| Headache | 9.6 | 7.9 | 5.6 |
| Dyspepsia | 6.5 | 0.9 | 1.7 |
| Vomiting | 6.5 | 3.5 | 0.4 |
| **Add-on to Metformin + Rosiglitazone** | | | |
| | All Victoza® + Metformin + Rosiglitazone N = 355 | Placebo + Metformin + Rosiglitazone N = 175 | |
| **Adverse Reaction** | (%) | (%) | |
| Nausea | 34.6 | 8.6 | |
| Diarrhea | 14.1 | 6.3 | |
| Vomiting | 12.4 | 2.9 | |
| Headache | 8.2 | 4.6 | |
| Constipation | 5.1 | 1.1 | |

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

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

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

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

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

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

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

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

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** 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. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; Angioedema and anaphylactic reactions; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

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

**More detailed information is available upon request.**

For information about Victoza® contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1–877-484-2869

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



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VICTOZA®
liraglutide (rDNA origin) injection

# Victoza®—a force for change in type 2 diabetes.


A 52-week, double-blind, double-dummy, active-controlled, parallel-group, multicenter study. Patients with type 2 diabetes (N=745) were randomized to receive once-daily Victoza® 1.2 mg (n=251), Victoza® 1.8 mg (n=246), or glimepiride 8 mg (n=248). The primary outcome was change in A1C after 52 weeks.

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VICTOZA®
liraglutide (rDNA origin) injection

## Indications and Usage

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

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.

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Victoza® has not been studied in combination with prandial insulin.

## 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.**

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

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

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during postmarketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

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, dyspepsia, constipation and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

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

There is limited data in patients with renal or hepatic impairment.

In a 52-week monotherapy study (n=745) with a 52-week extension, the adverse reactions reported in ≥ 5% of patients treated with Victoza® 1.8 mg, Victoza® 1.2 mg, or glimepiride were constipation (11.8%, 8.4%, and 4.8%), diarrhea (19.5%, 17.5%, and 9.3%), flatulence (5.3%, 1.6%, and 2.0%), nausea (30.5%, 28.7%, and 8.5%), vomiting (10.2%, 13.1%, and 4.0%), fatigue (5.3%, 3.2%, and 3.6%), bronchitis (3.7%, 6.0%, and 4.4%), influenza (11.0%, 9.2%, and 8.5%), nasopharyngitis (6.5%, 9.2%, and 7.3%), sinusitis (7.3%, 8.4%, and 7.3%), upper respiratory tract infection (13.4%, 14.3%, and 8.9%), urinary tract infection (6.1%, 10.4%, and 5.2%), arthralgia (2.4%, 4.4%, and 6.0%), back pain (7.3%, 7.2%, and 6.9%), pain in extremity (6.1%, 3.6%, and 3.2%), dizziness (7.7%, 5.2%, and 5.2%), headache (7.3%, 11.2%, and 9.3%), depression (5.7%, 3.2%, and 2.0%), cough (5.7%, 2.0%, and 4.4%), and hypertension (4.5%, 5.6%, and 6.9%).

**Please see brief summary of Prescribing Information on adjacent page.**


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