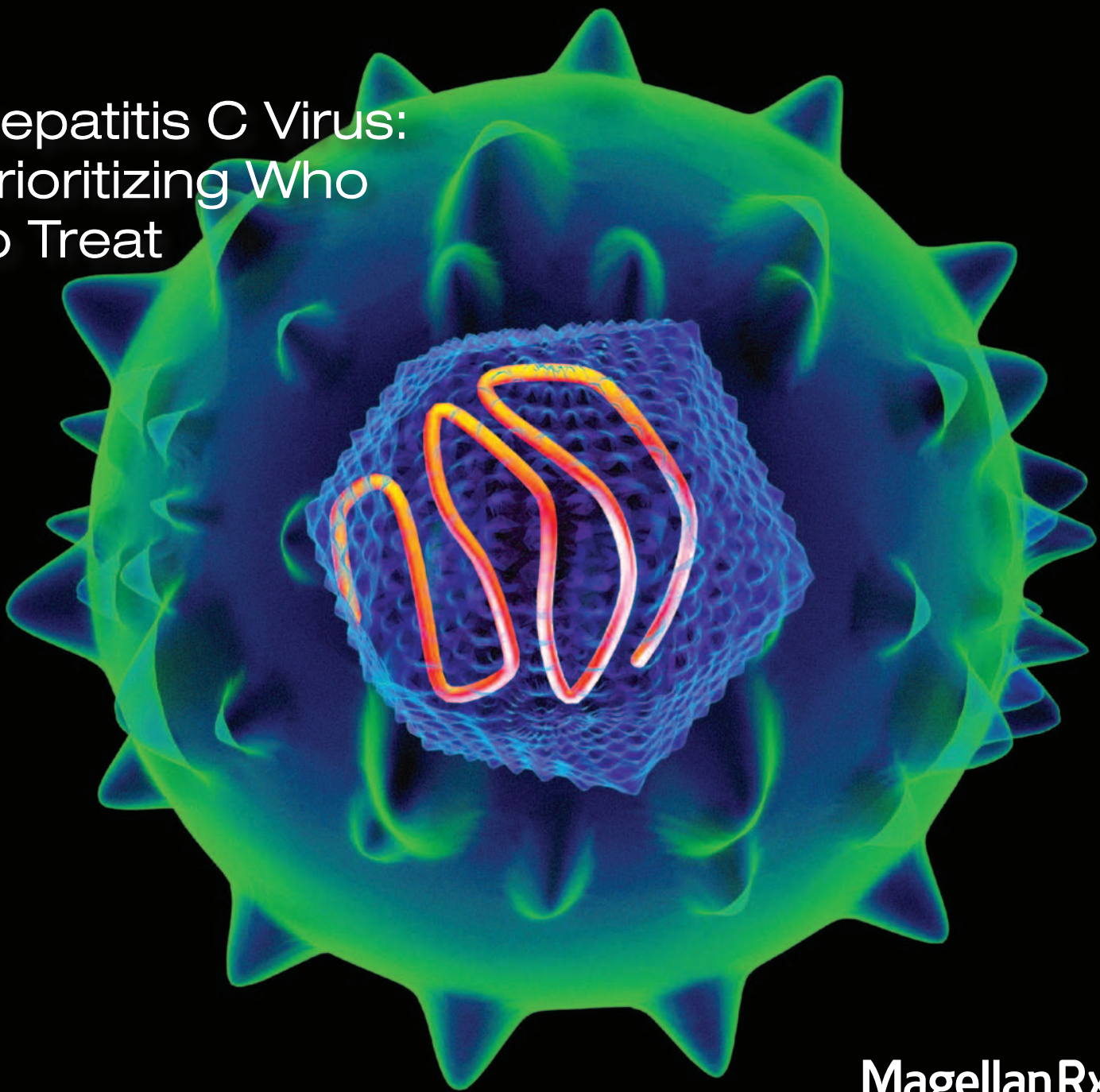
Fall 2014



# Magellan Rx Report

## MEDICAL AND PHARMACY BENEFIT MANAGEMENT

## Hepatitis C Virus: Prioritizing Who to Treat



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# WELCOME

to this issue

## features



## trends

# Letter from Magellan Rx

## Dear Managed Care Colleagues,

Susan Petrovas, RPh

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

As everyone within the managed care industry is acutely aware, the cost associated with specialty pharmaceuticals continues to be a major concern. Within the next five years, specialty drugs will represent half of the total drug spend for health insurance providers. Further complicating the increased cost burden is the fact that half of the specialty spend will fall under the medical benefit. It is important for health plans to have an accurate understanding of the future specialty marketplace and incorporate the right tools and strategies to not only manage the increasing drug spend, but also improve clinical outcomes.

At Magellan Rx Management, we're committed to providing our clients with a smarter approach to specialty benefit management. Our integrated solutions combine our medical, specialty, and pharmacy benefit expertise into one organization, allowing us to leverage our collective scale and experience in managing total drug spend for our payor clients, while ensuring a clear focus on the specific clinical/financial needs of each individual customer.

Magellan Rx Management has developed easy-to-use tools and insightful cost-saving solutions that are designed to improve the health of your members and customized based on your specific needs. In addition, we can provide an integrated analysis of plan-specific medical and pharmacy utilization to paint a more comprehensive picture of true clinical and financial outcomes to help health plans make more informed decisions. This type of analysis can be extremely insightful when evaluating the impact that various sites of care have on resource utilization and in the identification of management opportunities.

Magellan Rx Management is focused on the needs of our customers and is committed to providing our payor clients with the high standard of customer service that you have come to expect. If you have questions regarding any of the services offered by Magellan Rx Management, please feel free to contact me directly at **spetrovas@magellanhealth.com**. As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

Susan C. Petrovas, RPh
Magellan Rx Management

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# MANAGED CARE NEWSSTAND

## A First Step for Accountable Care

Great strides have been made in promoting patient-centered care. But a report in the *American Journal of Managed Care* said there should be a greater focus on helping patients select the physicians who best meet their needs, preferences, and values.

"Strengthening the attention to patient preferences in this critical first step of a patient's healthcare experience is critical if patients are going to become engaged partners in their care and form strong therapeutic alliances with their physicians," the report said.

The authors said these five factors should be considered when matching patients with physicians:

- Communication and decision-making style
- Therapeutic approach
- Social and cultural appropriateness
- Cost and value
- Practice environment

The authors said getting patients the information they need to evaluate these factors is an important step in moving toward a more patient-centered approach for physician selection.

*Source:* Powers B, Jain SH. Patient-centered physician selection: a necessary first step for accountable care. *Am J Manag Care*. Epub 20 June 2014. www.ajmc.com/publications/ajac/2014/2014-1-vol2-n2/patient-centered-physician-selection-a-necessary-first-step-for-accountable-care.

## Competition Heats Up for Zydelig® and Imbruvica®

The competition is heating up between two new cancer drugs. The U.S. Food and Drug Administration (FDA) recently approved the new blood cancer drug Zydelig® (idelalisib). It also got a recommendation for use in Europe from the Committee for Medicinal Products for Human Use (CHMP). Competitor Imbruvica® (ibrutinib) received FDA approval several months earlier, followed by an expanded FDA approval and the same recommendation from the CHMP.

Zydelig® is a first-in-class inhibitor of the PI3k delta protein that is overexpressed in many B-cell blood cancers. The FDA approved its use for three types of B-cell blood cancers. It was approved for use in the treatment of relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab (Rituxan®). The FDA granted an accelerated approval for Zydelig® use in treating patients with relapsed follicular B-cell non-Hodgkin's lymphoma and relapsed small lymphocytic lymphoma.

Imbruvica® recently received expanded FDA approval and breakthrough therapy designation to treat patients with CLL who have a deletion in chromosome 17 (17p deletion). Patients with this deletion may have a poor response to standard treatments. Previously, the FDA approved Imbruvica® for use in certain patients with mantle cell lymphoma (MCL) and CLL.

"In less than a year, we have seen considerable progress in the availability of treatments for chronic lymphocytic leukemia," said Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, in a news release.

*Sources:* U.S. Food and Drug Administration. FDA approves Zydelig for three types of blood cancers [news release]. 23 July 2014.
U.S. Food and Drug Administration. FDA expands approved use of Imbruvica for chronic lymphocytic leukemia [news release]. 28 July 2014.
Palmer E. Gilead's Zydelig, J&J's Imbruvica will go toe-to-toe in EU with nod for CLL. FiercePharma. 25 July 2014. www.fiercepharma.com/story/gileads-zydelig-jjs-imbruvica-will-go-toe-toe-eu-nod-cll/2014-07-25.
Gilead Sciences, Inc. U.S. Food and Drug Administration approves Gilead's Zydelig (idelalisib) for relapsed chronic lymphocytic leukemia, follicular lymphoma and small lymphocytic lymphoma [news release]. 23 July 2014.

## Pricey Cholesterol Drugs Causing Concern

New potentially groundbreaking drugs for cholesterol have pharmacy benefit managers concerned about how they'll be able to contain rising healthcare costs.

A new class of cholesterol drugs called PCSK9 inhibitors is helping to control cholesterol in patients who do not respond to traditional treatments. The estimated cost of treatment with these injectable medications is about $10,000 a year. In addition, patients will need to take the medication for the rest of their lives.

While it's unlikely that this class of drugs will be approved for first-line therapy, it could be a welcome and effective option for patients with hard-to-treat cholesterol.

*Source:* Staton T. Payers fret about the next drug doomsday: pricey PCSK9 cholesterol meds. FiercePharma. 7 May 2014. www.fiercepharmamarketing.com/story/payers-already-fretting-about-next-pharm-apocalypse-pricey-pcsk9-cholestero/2014-05-07.

## PD-1 Inhibitor Pembrolizumab Makes Major Headway

The U.S. Food and Drug Administration (FDA) has granted priority review designation to the application for pembrolizumab (MK-3475)—an investigational anti-PD-1 antibody—to treat patients with metastatic or inoperable melanoma who have already been treated with Yervoy® (ipilimumab). Earlier, the drug received the FDA's breakthrough therapy designation for the treatment of advanced melanoma.

Merck recently presented more than 15 abstracts and six talks at the 2014 American Society of Clinical Oncology Annual Meeting. Scientists presented clinical data from pembrolizumab studies on advanced melanoma, advanced non-small cell lung cancer, and advanced head and neck cancer.

One presentation revealed data from the largest ongoing phase 1b study evaluating the effectiveness of pembrolizumab as a monotherapy in 411 patients with advanced melanoma. The researchers found that after treatment the estimated overall survival rate (OS) at one year was 69 percent among all patients. Certain subgroups of patients had higher or lower OS rates. The estimated OS at 18 months was 62 percent.

"While we await further confirmation through controlled clinical trials, the survival rates seen with pembrolizumab therapy, including in patients with advanced disease who have failed other therapies, support the use of immune manipulation in cancer care," said Roger M. Perlmutter, MD, PhD, President of Merck Research Laboratories, in a news release.

Researchers are studying the effectiveness of pembrolizumab as a sole therapy and as combined therapy in the treatment of 30 tumor types. By the end of 2014, Merck estimates that more than 24 clinical trials involving about 6,000 patients will be under way at nearly 300 sites worldwide.

*Sources:* Merck. Data on Merck's pembrolizumab from largest study to date of investigational anti-PD-1 antibody in advanced melanoma highlighted at ASCO 2014 [news release]. 2 June 2014.

Merck. Merck announces FDA acceptance for review of MK-3475 Biologics License Application for advanced melanoma [news release]. 6 May 2014.

## Pharmacy Benefit Management—What's Driving Change?

How is healthcare reform affecting pharmacy benefit management? Researchers conducted a Delphi study with 11 pharmacy leaders to identify the drivers of change in pharmacy benefit management over the next few years. After responding to the initial questions, the pharmacy leaders reviewed the findings to reach a consensus.

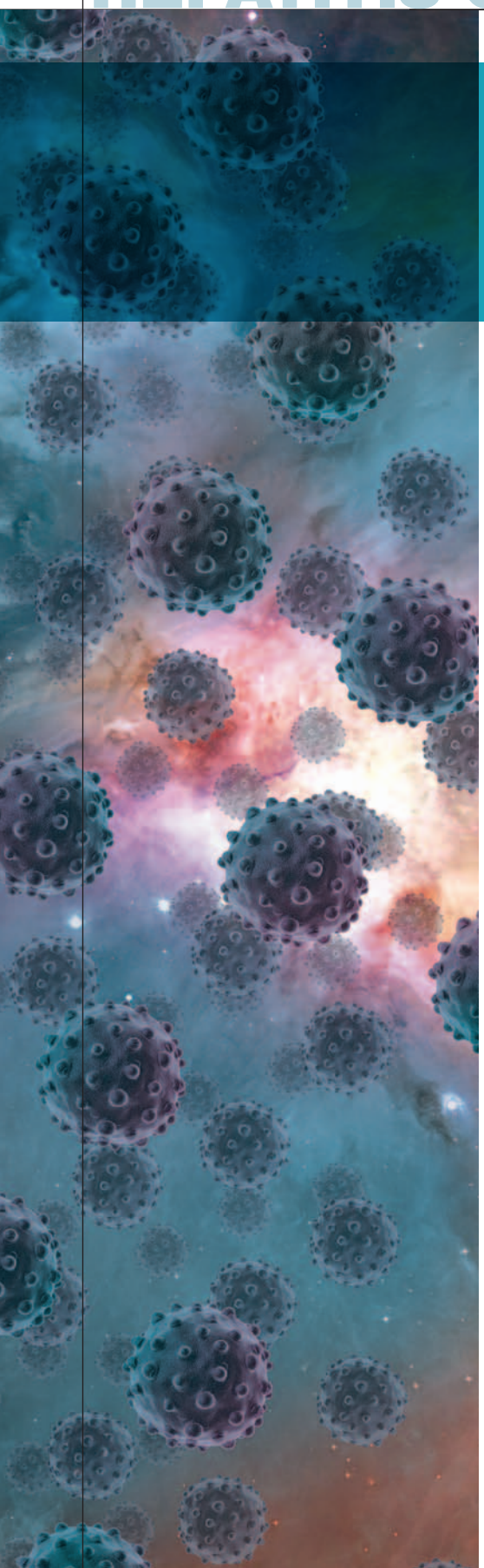
Here are some of the significant findings:

- The role of pharmacy is becoming more important.
- Pharmacists will become integral members of patient care teams.
- Doctors will rely more on pharmacy.
- Integration of medical and pharmacy data will become vital.
- Healthcare reform will offer opportunities to enhance the role of managed care pharmacies.

The study also noted the importance of integrating medical care and pharmacy to "create economically sustainable drug benefit management programs for the future."

The researchers said that these managed care techniques may help pharmacy benefit management weather the changes coming as a result of healthcare reform: integrated care programs, narrow pharmacy networks, medication therapy management, management of specialty medication costs, and pay-for-performance models.

*Source:* Berger J, et al. Drivers of change in pharmacy benefit management. *Am J Pharm Benefits*. 2014;6(3):124-128. www.ajmc.com/publications/ajpb/2014/AJPB_MayJune2014/Drivers-of-Change-in-Pharmacy-Benefit-Management.



# Hepatitis C Virus: Identifying Patients at High Risk for Disease Progression

*Scott McClelland, PharmD, Senior Director of Pharmacy, Florida Blue*
*Semy Lee, PharmD Candidate, University of Rhode Island*

Scott McClelland, PharmD

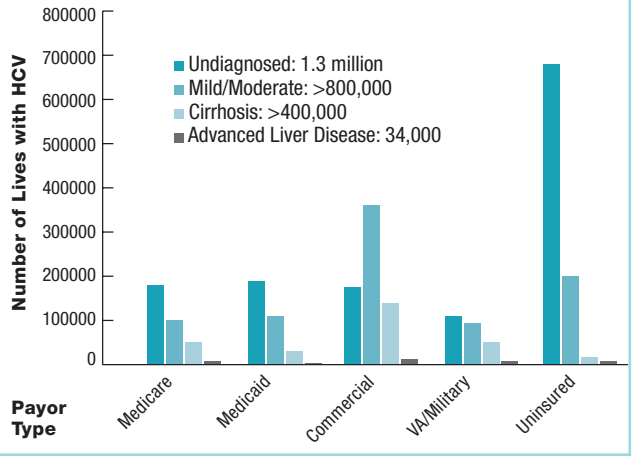
Hepatitis C virus (HCV) is the most common chronic bloodborne infection in the United States, with approximately 3.2 million people currently infected.[1] In 2011, health plan expenditures associated with HCV drastically increased following the FDA approval of two protease inhibitors, telaprevir (Incivek®) and boceprevir (Victrelis®).[2,3] These products, in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV), were quickly recognized as the gold standard of treatment for genotype 1 HCV. However, this was short-lived. Almost immediately following the FDA approval of sofosbuvir (Sovaldi®),[4] a first-in-class nucleotide analog inhibitor, the American Association for the Study of Liver Diseases (AASLD) modified its guidelines to recommend Sovaldi,® in combination with Peg-IFN and RBV, as the treatment of choice when initiating therapy in treatment-naïve patients.[5] Although this recommendation was supported by response rates that were unmatched by any other published trial to date, the cost of Sovaldi® therapy has generated even greater economic concerns within the managed care industry. In addition, several all-oral therapies are nearing FDA approval and are anticipated to become available by the end of 2014. This generates two important questions that managed care organizations are quickly trying to answer: 1) how much will these new therapies cost per patient and 2) how many patients are going to require treatment?

In order for managed care organizations to accurately forecast HCV-related costs, it is important to understand the various patient populations chronically infected with HCV, the number of patients currently diagnosed and under the care of a hepatologist/gastroenterologist, and characteristics that place certain patients at a higher risk for disease progression. Understanding these components can help health plans estimate the number of patients within their networks that are likely to request treatment and identify high-risk patients who, without HCV therapy, are more likely to progress and generate greater long-term costs associated with decompensated liver disease, cirrhosis, and transplant.

## Current Breakdown of HCV Patients in the United States

Although there are 3 to 5 million patients estimated to be chronically infected with HCV, less than half of this population is diagnosed.[6] Currently, this epidemic is concentrated in the baby boomer generation, with the bulk of the infected population becoming eligible for Medicare over the next 10 years. The large majority of these patients contracted HCV over 30 years ago and, without treatment, will

**Figure 1: 2013 HCV Populations by Payor Type and Disease Severity[8]**




likely develop fibrosis, cirrhosis, advanced liver disease, or hepatocellular carcinoma (HCC).[7] In addition, with the reduction of the uninsured population as a result of healthcare reform and recent recommendations for increased HCV screening, the number of diagnosed patients is expected to grow. With this in mind, the financial burden to the U.S. healthcare system is a major concern for insurance providers. For health plans to prioritize the most appropriate patients for immediate HCV therapy, it is important to understand the various subpopulations of HCV patients who are at the highest risk of disease progression and, most likely, associated with a greater potential for expensive liver complications.

## HCV Patients at High Risk for Disease Progression

Questions that many health plans have been asking since the spike in HCV-related expenditure are, "Which patients need to be treated now and which patients can safely wait?" The answers to these questions are largely related to the individual risk of disease progression for each patient. In fact, patients can be infected for decades without developing permanent liver damage. However, if left untreated, HCV slowly causes long-term liver damage, ultimately causing cirrhosis and HCC.[7] Therefore, it is critical to treat the infection before patients develop liver complications that further increase the economic burden associated with the disease.

For payors, it is important to understand the HCV patient populations that are at the highest risk of rapid disease progression and ensure that these patients receive priority treatment. The identification and treatment of these patients before presentation of advanced liver complications can prevent long-term and unnecessary HCV-related cost. The following patient populations with HCV are at the greatest risk of disease progression and should be considered appropriate candidates for antiviral therapy:

- Patients with advanced liver disease and post-liver transplant
- Genotype 3 patients
- Patients with HIV coinfection

## Patients with Advanced Liver Disease and Post-Liver Transplant

Once end-stage liver disease develops, transplantation becomes the only treatment option to extend patient survival. In the United States, HCV infection is the most common cause of liver transplantation.[7,9] Unfortunately, HCV recurrence rates in post-transplant patients are high and these patients tend to progress more rapidly to advanced liver disease. HCV infection has been shown to significantly reduce not only patient survival, but also the survival of the donor liver following liver transplantation.[10] In addition to low survival rates, studies have shown that chronic HCV progresses more rapidly post-transplantation, with a median duration to cirrhosis of only 10 years, compared with several decades in newly infected patients.[11]

This data indicates that HCV patients who are candidates for liver transplantation (i.e., advanced cirrhosis/decompensated liver disease) and those with active HCV following transplant should be prioritized for HCV treatment. If the infection is cured before the liver transplantation, the likelihood of recurrence is greatly reduced and post-transplant outcomes are improved. Another important consideration is the management of patients prior to the need for transplant. Treating patients with compensated cirrhosis and achieving a sustained response could prevent the need for liver transplantation, thereby minimizing unnecessary costs.

With the reduced survival rate associated with HCV post-transplant and the rapid progression of HCV-related complications in this population, early treatment of these patients is critical to improve outcomes and contain unnecessary costs. Whenever possible, it is also important to minimize the number of patients requiring liver transplantation due to HCV by allowing appropriate medication access to patients at high risk of disease progression (e.g., cirrhotic patients).

## Genotype 3 Patients

HCV is classified into 11 genotypes with many subtypes, and the cure rate and progression rate differ for each genotype. In the United States, genotype 1 is the most prevalent and therefore most new therapies anticipating FDA approval

## American Association for the Study of Liver Diseases (AASLD): When and in Whom to Initiate HCV Therapy

| Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment Is Most Likely to Provide the Most Immediate and Impactful Benefits |
|---|
| **Highest Priority for Treatment (Class I Evidence Only)** |
| • Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)<br>• Organ transplant<br>• Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations |
| **High Priority for Treatment (Class I Evidence Only)** |
| • Fibrosis (Metavir F2)<br>• HIV coinfection |

| Persons Whose Risk of HCV Transmission Is High and in Whom HCV Treatment May Yield Transmission Reduction Benefits |
|---|
| **High HCV Transmission Risk (Class IIa Evidence)** |
| • MSM with high-risk sexual practices<br>• Active injection drug users<br>• Incarcerated persons<br>• Persons on long-term hemodialysis |

| Additional AASLD Recommendations |
|---|
| • An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended (class I evidence) |
| • Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred (class I evidence) |

| Factors Associated with Accelerated Fibrosis Progression | |
|---|---|
| **Non-Modifiable** | **Modifiable** |
| • Fibrosis state<br>• Genotype 3<br>• Coinfection with HBV or HIV<br>• Older age at time of infection<br>• Male sex<br>• Organ transplant | • Alcohol consumption<br>• Nonalcoholic fatty liver disease<br>• Obesity<br>• Insulin resistance |

*Source:* American Association for the Study of Liver Diseases. When and in whom to initiate HCV therapy. August 2014. www.hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy.

are focused around treating the genotype 1 patient population. Although it is generally considered more difficult to achieve a sustained response for genotype 1 HCV, recent studies have found that genotype 3 patients are more likely to progress to advanced liver disease, including faster development of cirrhosis.[12,13] Genotype 3 patients have been shown to be 31 percent more likely to develop cirrhosis and 80 percent more likely to develop HCC compared to patients with genotype 1 HCV.[13] Within managed care, genotype 3 is often overlooked, with a greater focus placed on genotype 1 patients. However, with the accelerated progression observed in this population, pharmacotherapy should be strongly considered in patients with genotype 3 HCV.

## HIV/HCV Coinfection

HCV can have a significant impact on patients who are coinfected with HIV. HIV patients can now live near normal lifespans with the availability of highly active antiretroviral therapy (HAART). However, when they are coinfected with HCV, mortality rates increase due to the HCV-related liver complications. Liver-associated mortality is the major cause of death in coinfected patients, and considering that all cases of liver-related death among HIV patients occurred in HIV/HCV-coinfected patients, the liver damage is thought to be solely caused by the HCV infection.[14] In addition, liver disease progression is accelerated in coinfected patients compared with HCV-monoinfected patients.[15] Compared with HCV-

monoinfected patients, coinfected patients develop cirrhosis 12 years earlier.[16] Most of the time, coinfected patients acquire HCV first. Those who acquire HIV before they acquire HCV, however, can have more aggressive liver disease progression. Recently coinfected patients show moderate to severe fibrosis within only several months, even with no additional risk factors.[17] The mechanism for this accelerated progression is not well understood, but the evidence seems to be clear that the preexisting HIV can exacerbate HCV liver damage progression. With these patients at an increased risk of disease progression, appropriate therapy should be initiated to prevent advanced liver disease and increased liver-related mortality.

## Additional Managed Care Considerations

In a world with unlimited resources, it would be ideal to treat all patients with HCV upon diagnosis. However, with the restraints of the current healthcare system, budgetary limitations exist that must be considered. To ensure treatment for the most appropriate patients and utilize resources wisely, managed care organizations need to understand the risk of disease progression associated with the various patient types. HCV is not homogenous and neither are the patients who are infected. Although the financial risks of treating patients have stolen the spotlight in recent years, it is important to also consider the clinical and economic risks of allowing high-risk patients to go untreated.

Some patient groups, such as those with a Metavir fibrosis score of F0 to F2, are unlikely to develop cirrhosis in the near future compared with those in more advanced stages. After assessing for other risk factors that may increase disease progression, it may be acceptable to delay treatment in patients at low risk. However, it is important to remember that fibrosis score is relatively subjective and based on clinician judgment. It can be very difficult to differentiate between Metavir scores F2 and F3. Many providers that specialize in HCV recommend against using a Metavir score of F3 as the primary determinant when evaluating coverage decisions. In addition, it is important to remember that liver biopsy is no longer the only method of diagnosing cirrhosis. Noninvasive laboratory tests that are significantly correlated with fibrosis/cirrhosis are available. Therefore, prior authorization criteria for HCV therapy that require liver biopsy may be modified to include more cost-effective options for diagnosing cirrhosis.

For all patients initiating therapy, it is important to assess patient readiness. There are tools available to evaluate the readiness of patients for HCV treatment. High treatment success rates require adherence to medications. If the patient is not ready to commit to the entire treatment duration and withstand the problematic side effects, then premature discontinuation and treatment failure are likely. Also, if patients are current users of injectable illicit drugs, then lifestyle modification before the initiation of therapy is required to prevent HCV reinfection following treatment.

Unfortunately, it is difficult to determine which patients require therapy first and which patients are appropriate to delay. However, those who are at a greater risk of developing severe liver damage and those who are already in the advanced stages of liver disease should be considered appropriate candidates to initiate therapy. Those who are at relatively early stages without any other risk factors may actually benefit by delaying therapy and waiting for the availability of future treatment options. In the meantime, more drugs are being developed and coming to market, and the cure rate for HCV is increasing as well. Although the financial implications associated with HCV therapies are likely to exist well into the 2020s, the clinical outcomes associated with new HCV therapies are, without a doubt, impressive, and the next 10 years will likely be a defining time for the clinical management of HCV.

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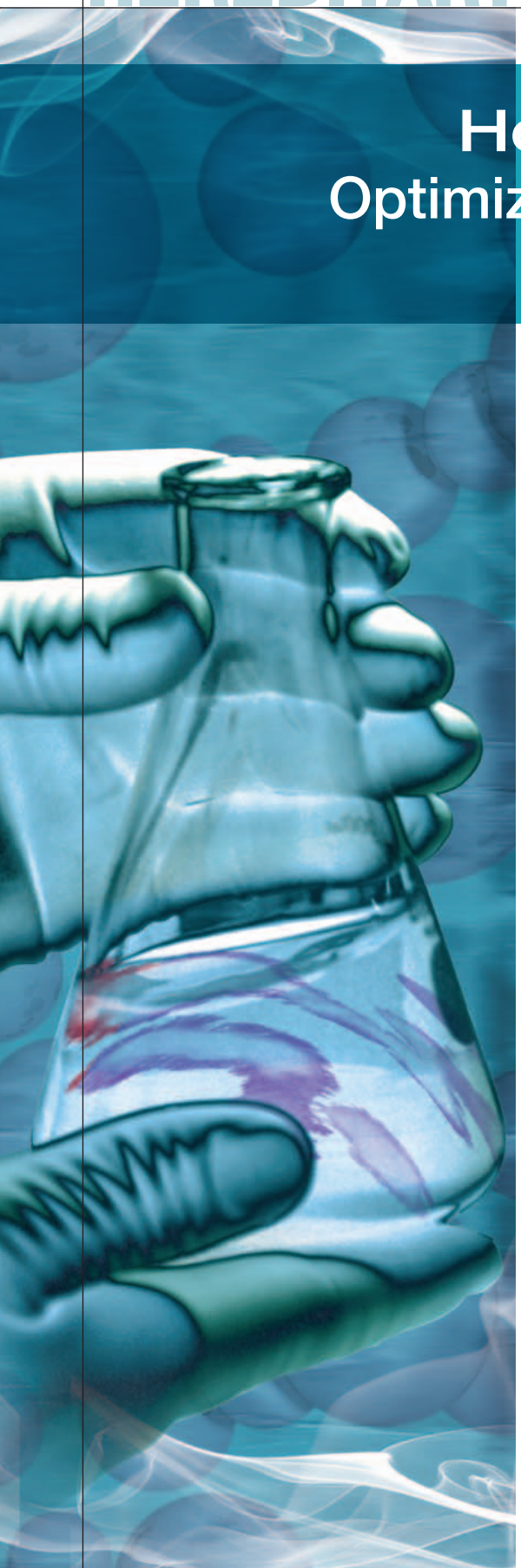
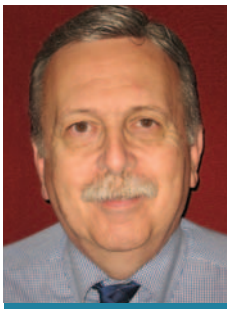


# Hereditary Angioedema: Optimizing Management Strategies

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



William J. Cardarelli, PharmD

Hereditary angioedema (HAE) is a rare disorder caused by a genetic mutation that results in either inadequate levels of, or defective, C1 inhibitor (C1-INH) protein.[1] This disease leads to an increase in bradykinin, ultimately resulting in episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema. Symptoms of HAE typically begin in early childhood (2 to 3 years of age) and may involve a wide variety of body parts (including tongue and larynx). These "attacks" of symptoms occur on average every 7 to 14 days in untreated patients and can be precipitated by minor trauma and stress, but may occur without an apparent trigger as well. The incidence of HAE is approximately 1 in 30,000 to 50,000.[1-3]

Three variants of HAE have been identified. HAE type I, which represents approximately 80 to 85 percent of HAE cases, results from insufficient production of the C1-INH protein.[1,3] There is usually a family history of angioedema that is associated with type I HAE, but a number of cases are due to a spontaneous mutation of the chromosome 11 gene. HAE type II, which represents approximately 15 to 20 percent of HAE cases, is caused by production of defective or dysfunctional C1-INH protein.[1,3] Both types I and II HAE are due to insufficient levels of blood C1-INH protein and both are associated with attacks of angioedema. HAE type III, or also known as HAE with normal C1-INH, represents less than 1 percent of HAE cases. Patients with type III HAE have normal levels of C1-INH protein, but have a specific mutation in the coagulation factor XII gene.[1-3] HAE type III is predominantly reported in women, where swelling may be associated with pregnancy and the use of estrogen-containing oral contraceptives. The underlying pathophysiology of HAE type III is unlike types I and II; hence, the management may be different since it cannot be assumed that the therapies used to treat types I and II will respond similarly to type III.[2]

## Treatment of HAE

Generally, HAE does not respond to the usual treatment for allergic angioedema, including antihistamines, epinephrine, or glucocorticoids. Effective management of HAE is targeted to either treating attacks using "on-demand" therapy or preventing attacks using short-term prophylaxis (administered in

the expectation of a potential swelling event) or long-term prophylaxis. On-demand treatments are given at the onset of symptoms to relieve the angioedema, and prophylactic treatments are given at regular intervals to either reduce the likelihood of swelling in a patient undergoing a stressor, or to decrease the number and severity of angioedema attacks overall.[1]

Physical trauma and stress are well-known precipitants of HAE attacks. Dental surgery in particular is associated with swelling of the oral cavity that can cause airway obstruction.[1,2] The exact risk associated with swelling after these procedures is not well known, but evidence suggests that short-term prophylaxis has been associated with a reduction in the incidence of swelling for both adults and children. A large retrospective study found that the risk of swelling was 21.5 percent in patients who did not receive any prophylaxis. The risk of swelling fell to 16 percent and 7.5 percent in patients who received 500 or 1,000 units of C1-INH, respectively, one hour before a dental extraction.[4]

Due to the wide variability of the disease, patient-specific factors and the type of procedure should be considered to determine whether prophylaxis is needed. In some cases, long-term prophylaxis with the use of regular medication to prevent episodes of angioedema can be considered. Cinryze® is the only C1-INH indicated for routine prophylaxis against angioedema attacks in adults and adolescents.[5] Androgens such as danazol have been shown to be effective in preventing attacks, but due to the numerous side effects, careful surveillance is needed.[2] The U.S. Hereditary Angioedema Association (HAEA) Medical Advisory Board states that androgens should not be used in patients who express a preference for an alternative therapy and failure to androgen therapy should not be a prerequisite to receiving prophylactic C1-INH.[1] Tranexamic acid, a competitive inhibitor of plasminogen activation, has been used for short-term preprocedural prophylaxis in the past, but the efficacy in suppressing breakthrough attacks is low.[2]

Five total products are available in the U.S. market for HAE (Table 1). While Cinryze® is approved for routine prophylaxis against angioedema attacks, Berinert®, Kalbitor®, Firazyr®, and the recently approved recombinant C1-INH product Ruconest® are approved for the treatment of acute attacks of HAE.[6-8] There are no clear advantages of using one agent over the other, since there are no head-to-head trials or laboratory tests to indicate which medications are more appropriate for certain patients.[1] The side effect profile and the frequent monitoring that is necessary with the androgen therapy put the new therapies at an advantage.

## Guideline Recommendations

Due to the wide variability of the disease among patients, treatment strategies must be individualized based on patient-specific factors and preferences.[1] The World Allergy Organization (WAO) recommends that all attacks that result in debilitation/dysfunction and/or involve the face, neck, or abdomen should be considered for on-demand treatment, and that treatment of attacks affecting the upper airways be mandatory.[2] Although abdominal attacks are painful and peripheral attacks can result in impaired function, attacks of the upper airways can result in asphyxiation. By using on-demand treatment as early

**Table 1 Products Available for Hereditary Angioedema in the United States[5-9]**

| Treatment | Indication | Class | Dose | Cost |
|---|---|---|---|---|
| Cinryze® (C1 esterase inhibitor [human]) | Prophylaxis in adolescents and adults | C1-inhibitor | 1,000 units intravenous (IV) infusion every 3-4 days | $2,453/500 units |
| Berinert® (C1 esterase inhibitor [human]) | Acute attacks in adolescents and adults | C1-inhibitor | 20 units/kg slow IV injection | $2,414/500 units |
| Kalbitor® (ecallantide) | Acute attacks in ≥12 years old | Human plasma kallikrein inhibitor | 30 mg subcutaneously (SC) (in 3 divided doses) once, repeat every 6 hours as needed (max 60 mg/day) | $11,130/30 mg |
| Firazyr® (icatibant) | Acute attacks in ≥18 years old | Bradykinin B2 receptor antagonist | 30 mg SC once, repeat every 6 hours as needed (max 90 mg/day) | $8,005/30 mg |
| Ruconest® (conestat alfa) | Acute attacks in adolescents and adults | Recombinant C1-inhibitor | 50 units/kg (ABW ≥ 84 kg) or 4,200 units (ABW ≤ 84 kg) IV once | Recently approved—not yet available |

as possible in these circumstances, the severity of the attacks and the amount of medication needed to offset the attacks can be minimized.[1,2]

Currently, there are no studies specifically designed to assess the risk-benefit of long-term prophylactic treatment versus on-demand treatment. The Hereditary Angioedema International Working Group (HAWK) suggests on-demand treatment to be the initial option for treating acute attacks due to the evidence of avoiding mortality and reducing morbidity.[10] Long-term prophylaxis may be appropriate for patients in whom on-demand treatment is unable to minimize the suffering related to the disease. It has been suggested to consider long-term prophylaxis when patients, despite if episodes are controlled with the use of on-demand treatment, continue experiencing more than 12 moderate-to-severe attacks per year or have more than 24 days per year affected by HAE.[10] As always, patient-specific factors such as attack frequency, attack severity, comorbid conditions, access to emergency treatment, and patient preference should be considered before initiating long-term prophylaxis.[1,10]

## Pharmacoeconomic Considerations

Both indirect and direct costs associated with HAE must be considered in order to understand the cost-effectiveness of new agents. Average annual direct medical costs are $25,884 per patient, of which $21,339 (82.4 percent) is the cost of medical treatment for acute attacks (routine care outside of acute treatment accounts for the remaining $4,545).[11] As expected, the cost associated with an attack is directly proportional to the severity; the more severe the attack, the higher the cost. Furthermore, emergency room visits and hospital stays for acute attacks account for almost half of all direct costs.[11] By implementing more aggressive use of HAE therapies, there may be an opportunity to minimize costs associated with worsening attacks and hospital visits and therefore overall expenditure.

## Implications to Managed Care

The new therapies for HAE offer hope for patients to control their symptoms and increase their quality of life, which has been a significant challenge in the past. There is potential for using the new therapies for prophylactic measures in hopes of reducing the number and severity of attacks.[11] However, the high costs of these medications and a wide variability in response among individuals present a challenge. It is certain that treating acute attacks early is associated with better response to treatment. Optimizing patients on on-demand therapy prior to resorting to prophylaxis therapy may also be a significant savings opportunity for health plans. Educating patients about HAE plays an important role as well: Avoiding triggering factors, keeping detailed records of attacks, and knowing what to do in emergency situations will help lead to better health-related outcomes, including reductions in ED visits, hospitalizations, and severity of attacks, which can ultimately reduce costs. Greater utilization of home- and self-administration of select HAE therapies may provide further cost benefits as well. In order to maximize the cost-effectiveness of current therapies, careful patient selection for prophylactic and/or on-demand therapy is critical for success.

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In mCRPC therapy...

# Is there more to the story?


once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

## INDICATION

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

## IMPORTANT SAFETY INFORMATION

**Contraindications**—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

**Adverse Reactions**—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.

**Increased ZYTIGA® Exposures With Food**—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone $C_{max}$ and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

**Adrenocortical Insufficiency (AI)**—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

**Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess**—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

mCRPC=metastatic castration-resistant prostate cancer; AST=aspartate aminotransferase; ALT=alanine aminotransferase.

**Please see additional Important Safety Information on the next page.**
**Please see brief summary of full Prescribing Information on subsequent pages.**

For men with mCRPC who progressed on ADT

## In a clinical trial, patients had a median overall survival on ZYTIGA® (abiraterone acetate) of...*

# More than 1,000 days. And every day tells a story.

**35.3 MONTHS MEDIAN OVERALL SURVIVAL FOR ZYTIGA®** plus prednisone† vs **30.1 MONTHS** with placebo plus prednisone (active compound).‡

**5.2 MONTHS IMPROVEMENT IN MEDIAN OVERALL SURVIVAL** compared with placebo plus prednisone.

**Co-primary end point—overall survival: hazard ratio (HR)=0.792; 95% CI: 0.655, 0.956; *P*=0.0151; prespecified value for statistical significance not reached.**

**Co-primary end point—radiographic progression-free survival: median not reached for ZYTIGA® plus prednisone vs a median of 8.28 months for placebo plus prednisone. HR=0.425; 95% CI: 0.347, 0.522; *P*<0.0001.**

**IMPORTANT SAFETY INFORMATION (cont)**

**Increased ZYTIGA® Exposures With Food**—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone $C_{max}$ and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

**Hepatotoxicity**—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

***Study Design:** ZYTIGA®, in combination with prednisone, was evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with mCRPC who had not received prior chemotherapy (N=1,088). Patients were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In the ZYTIGA® arm, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the placebo arm, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In this study, the co-primary efficacy end points were overall survival (OS) and radiographic progression-free survival.

ADT=androgen-deprivation therapy.

Janssen Biotech, Inc.



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**Please see brief summary of full Prescribing Information on subsequent pages.**


**Drug Interactions**—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. *In vitro*, ZYTIGA® inhibits CYP2C8. There are no clinical data on the use of ZYTIGA® with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

**Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

†At a prespecified interim analysis for OS, 37% (200/546) of patients treated with ZYTIGA® plus prednisone compared with 43% (234/542) of patients treated with placebo plus prednisone had died.

‡Prednisone, as a single agent, is not approved for the treatment of prostate cancer.

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**ZYTIGA® (abiraterone acetate) Tablets**

Brief Summary of Prescribing Information.

## INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

## CONTRAINDICATIONS

**Pregnancy:** ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

## WARNINGS AND PRECAUTIONS

**Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess:** ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

**Adrenocortical Insufficiency:** Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

**Hepatotoxicity:** In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

**Increased ZYTIGA Exposures with Food:** ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone $C_{max}$ and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.



## ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.
- Increased ZYTIGA Exposures with Food *[see Warnings and Precautions]*.

**Clinical Trial 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 clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

**Study 1: Metastatic CRPC Following Chemotherapy:** Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

**Table 1: Adverse Reactions due to ZYTIGA in Study 1**

| | ZYTIGA with Prednisone (N=791) | | Placebo with Prednisone (N=394) | |
|---|---|---|---|---|
| **System/Organ Class** | All Grades[1] | Grade 3-4 | All Grades | Grade 3-4 |
| Adverse reaction | % | % | % | % |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Joint swelling/ discomfort[2] | 29.5 | 4.2 | 23.4 | 4.1 |
| Muscle discomfort[3] | 26.2 | 3.0 | 23.1 | 2.3 |
| **General disorders** | | | | |
| Edema[4] | 26.7 | 1.9 | 18.3 | 0.8 |
| **Vascular disorders** | | | | |
| Hot flush | 19.0 | 0.3 | 16.8 | 0.3 |
| Hypertension | 8.5 | 1.3 | 6.9 | 0.3 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 17.6 | 0.6 | 13.5 | 1.3 |
| Dyspepsia | 6.1 | 0 | 3.3 | 0 |
| **Infections and infestations** | | | | |
| Urinary tract infection | 11.5 | 2.1 | 7.1 | 0.5 |
| Upper respiratory tract infection | 5.4 | 0 | 2.5 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 10.6 | 0 | 7.6 | 0 |
| **Renal and urinary disorders** | | | | |
| Urinary frequency | 7.2 | 0.3 | 5.1 | 0.3 |
| Nocturia | 6.2 | 0 | 4.1 | 0 |
| **Injury, poisoning and procedural complications** | | | | |
| Fractures[5] | 5.9 | 1.4 | 2.3 | 0 |
| **Cardiac disorders** | | | | |
| Arrhythmia[6] | 7.2 | 1.1 | 4.6 | 1.0 |
| Chest pain or chest discomfort[7] | 3.8 | 0.5 | 2.8 | 0 |
| Cardiac failure[8] | 2.3 | 1.9 | 1.0 | 0.3 |

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

**Table 2: Laboratory Abnormalities of Interest in Study 1**

| | Abiraterone (N=791) | | Placebo (N=394) | |
|---|---|---|---|---|
| Laboratory Abnormality | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| Hypertriglyceridemia | 62.5 | 0.4 | 53.0 | 0 |
| High AST | 30.6 | 2.1 | 36.3 | 1.5 |
| Hypokalemia | 28.3 | 5.3 | 19.8 | 1.0 |
| Hypophosphatemia | 23.8 | 7.2 | 15.7 | 5.8 |
| High ALT | 11.1 | 1.4 | 10.4 | 0.8 |
| High Total Bilirubin | 6.6 | 0.1 | 4.6 | 0 |

**Study 2: Metastatic CRPC Prior to Chemotherapy:** Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

**Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2**

| | ZYTIGA with Prednisone (N=542) | | Placebo with Prednisone (N=540) | |
|---|---|---|---|---|
| **System/Organ Class** Adverse reaction | All Grades[1] % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| **General disorders** | | | | |
| Fatigue | 39.1 | 2.2 | 34.3 | 1.7 |
| Edema[2] | 25.1 | 0.4 | 20.7 | 1.1 |
| Pyrexia | 8.7 | 0.6 | 5.9 | 0.2 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Joint swelling/ discomfort[3] | 30.3 | 2.0 | 25.2 | 2.0 |
| Groin pain | 6.6 | 0.4 | 4.1 | 0.7 |
| **Gastrointestinal disorders** | | | | |
| Constipation | 23.1 | 0.4 | 19.1 | 0.6 |
| Diarrhea | 21.6 | 0.9 | 17.8 | 0.9 |
| Dyspepsia | 11.1 | 0.0 | 5.0 | 0.2 |
| **Vascular disorders** | | | | |
| Hot flush | 22.3 | 0.2 | 18.1 | 0.0 |
| Hypertension | 21.6 | 3.9 | 13.1 | 3.0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 17.3 | 0.0 | 13.5 | 0.2 |
| Dyspnea | 11.8 | 2.4 | 9.6 | 0.9 |
| **Psychiatric disorders** | | | | |
| Insomnia | 13.5 | 0.2 | 11.3 | 0.0 |
| **Injury, poisoning and procedural complications** | | | | |
| Contusion | 13.3 | 0.0 | 9.1 | 0.0 |
| Falls | 5.9 | 0.0 | 3.3 | 0.0 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 12.7 | 0.0 | 8.0 | 0.0 |
| Nasopharyngitis | 10.7 | 0.0 | 8.1 | 0.0 |

ZYTIGA® (abiraterone acetate) Tablets

**Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2 (continued)**

| | ZYTIGA with Prednisone (N=542) | | Placebo with Prednisone (N=540) | |
|---|---|---|---|---|
| **System/Organ Class** Adverse reaction | All Grades[1] % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| **Renal and urinary disorders** | | | | |
| Hematuria | 10.3 | 1.3 | 5.6 | 0.6 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash | 8.1 | 0.0 | 3.7 | 0.0 |

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

**Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2**

| | Abiraterone (N=542) | | Placebo (N=540) | |
|---|---|---|---|---|
| Laboratory Abnormality | Grade 1-4 % | Grade 3-4 % | Grade 1-4 % | Grade 3-4 % |
| Hematology | | | | |
| Lymphopenia | 38.2 | 8.7 | 31.7 | 7.4 |
| Chemistry | | | | |
| Hyperglycemia[1] | 56.6 | 6.5 | 50.9 | 5.2 |
| High ALT | 41.9 | 6.1 | 29.1 | 0.7 |
| High AST | 37.3 | 3.1 | 28.7 | 1.1 |
| Hypernatremia | 32.8 | 0.4 | 25.0 | 0.2 |
| Hypokalemia | 17.2 | 2.8 | 10.2 | 1.7 |

[1]Based on non-fasting blood draws

**Cardiovascular Adverse Reactions:** In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

**Post Marketing Experience**

The following additional adverse reactions have been identified during post approval use of ZYTIGA. 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.

*Respiratory, Thoracic and Mediastinal Disorders:* non-infectious pneumonitis.

## DRUG INTERACTIONS

**Drugs that Inhibit or Induce CYP3A4 Enzymes:** Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

**Effects of Abiraterone on Drug Metabolizing Enzymes:** ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the $C_{max}$ and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when

dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

*In vitro,* ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy: Pregnancy Category X** *[see Contraindications].:* ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

**Nursing Mothers:** ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

**Geriatric Use:** Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Patients with Hepatic Impairment:** The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions,* and *Clinical Pharmacology (12.3)] in full Prescribing Information.*

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**Patients with Renal Impairment:** In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

**OVERDOSAGE**

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

**Storage and Handling:** Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations]*.

**PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

**Manufactured by:**
Patheon Inc.
Mississauga, Canada

**Manufactured for:**
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Horsham, PA 19044



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### Program Integrity for Optimal Safety and Outcomes

Public Policy and Clinical Guidelines
Fraud, Waste & Abuse

# Treatment Options

Here are several FDA-approved treatment options for Genotype 1 Hepatitis C and the associated, estimated therapy costs.

Treatment Options

| Therapy Cost* | Preceding Treatment Options |
|---|---|
| $62,277 | Option #1[1] *(Victrelis [24 weeks] + Peginterferon + Ribavirin [28 weeks])* |
| $86,360 | Option #2[1†] *(INCIVEK® [12 weeks] + Peginterferon + Ribavirin [24 weeks])* |

| Therapy Cost* | New Standard of Therapy |
|---|---|
| $93,734 | Option #1[1] *(SOVALDI® + Ribavirin + Peginterferon [12 weeks])* |
| $170,462 | Option #2[1]-IFNI *(SOVALDI® + Ribavirin [24 weeks])* |

* *Cost calculated based on pharmacy reimbursement rates not reflecting any rebates*
1: *Genotype 1 Treatment Naïve patients with an early rapid virologic response*
1-IFNI: *Genotype 1 Patients ineligible to receive interferon*
† *As of October 16, 2014, Vertex Pharmaceuticals Incorporated will be discontinuing the sale and distribution of INCIVEK in the United States.*

## Pipeline

As this emerging topic continues to evolve, new treatment strategies and options will continue to become available. Expect another wave of new product alternatives in late 2014 and early 2015.Multiple direct-acting antivirals (DAAs) or new regimens for HCV are in the pipeline, with potential for being pangenotypic, interferon- and ribavirin-free, all-oral regimens.

Some contenders include AbbVie, BMS, BI, Gilead, and Janssen. Gilead is studying sofosbuvir (SOVALDI®) in various types of HCV patients including in genotype-1 treatment-naïve and experienced patients in combination with simeprevir (OLYSIO™) with and without ribavirin and in genotype-1 treatment-naïve and experienced patients, and as a fixed-dose combination with an investigational NS5A inhibitor agent, ledipasvir, with and without ribavirin. In surveys, some prescribers report that they would warehouse or defer treating patients, in anticipation of future DAAs.

The new wave of drugs represents an advance in the management of HCV with improvements in efficacy and tolerability. However, high cost, adverse effects, and drug interactions are likely to remain common.

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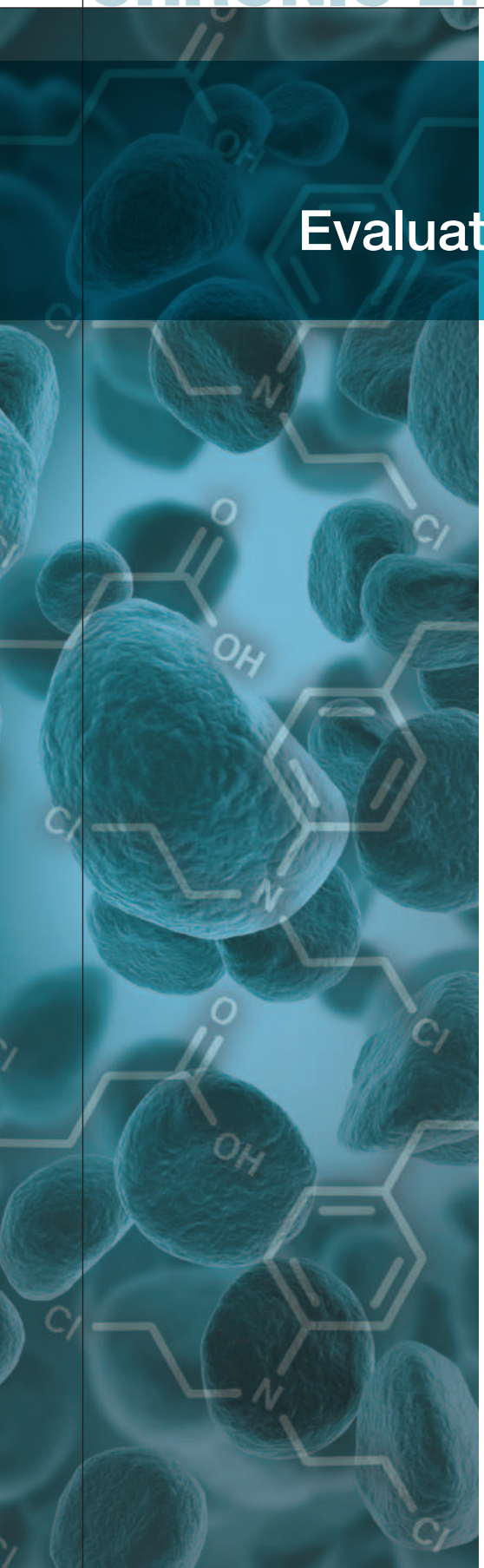
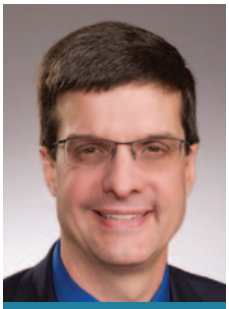


# The Changing Treatment Paradigm of CLL: Evaluation of Novel Treatment Options

*John Fox, MD, MHA, Associate Vice President of Medical Affairs, Priority Health*

## Introduction



John Fox, MD MHA

Chronic lymphocytic leukemia (CLL) is a rare blood disorder with a limited but growing number of effective treatment options. Although CLL is the most common adult leukemia in the United States, there were only about 15,600 patients diagnosed in 2013.[1,2] The annual incidence is projected to increase, as CLL is primarily a disease impacting elderly patients (median age at diagnosis is 72), a population that is steadily growing. The median survival for patients with CLL ranges from 8 to 12 years.[1,2] The variation is largely due to the severity/aggressiveness of the disease, presence of chromosomal abnormalities, and patient comorbidities.

About 25 percent of new patients with CLL are asymptomatic and are diagnosed incidentally from routine blood work.[3] The remaining 75 percent present a wide variety of nonspecific symptoms, such as unintentional weight loss, fever, and night sweats, making the diagnosis of CLL challenging based on symptoms alone.[3] CLL is usually only suspected following abnormal blood work showing a clonal population of small and mature lymphocytes detected in the peripheral blood. Because many patients with CLL are elderly and suffer from comorbid diseases, treatment is highly individualized and usually only indicated in patients with advanced disease (Rai stage III–IV) or significant disease burden.

## Staging and Prognosis of CLL

In the United States, the Rai system is mostly widely used to stage CLL. This system is based on the results from a physical examination and blood tests.[4] The Rai system is recommended by the National Comprehensive Cancer Network (NCCN) guidelines for determining therapy and stages patients from 0 to IV.[1,2] A modified version of the Rai system subdivides patients into three risk groups: low risk, intermediate risk, and high risk. Each level of risk is correlated with specific survival patterns (Table 1).[4]

In addition to the Rai stage, there are multiple other prognostic indicators for CLL survival. Immunoglobulin heavy chain variable (IgHV) mutational status plays a key role. Patients with the mutated IgHV have a more indolent clinical course and longer survival compared to those with unmutated IgHV.[5]

Two chromosomal mutations relay the greatest decrease in survival benefit: deletions in the short arm of chromosome 17, del(17p), and the long arm of chromosome 11, del(11q). Both mutations confer significant resistance to a number of available treatment options, signify aggressive disease, and are associated

**Table 1 Rai System for Staging of CLL[4]**

| Stage | Description | Risk Status | Median Survival (months) |
|---|---|---|---|
| 0 | Lymphocytosis, lymphocytes in blood >15,000/µL, and >40% lymphocytes in bone marrow | Low | 150 |
| I | Stage 0 with enlarged node(s) | Intermediate | 71-101 |
| II | Stage 0-I with splenomegaly, hepatomegaly, or both | | |
| III | Stage 0-II with hemoglobin <11 g/dL or hematocrit <35% | High | 19 |
| IV | Stage 0-III with platelets <100,000/µL | | |

with decreased survival.[1,2,6] Although several other mutations can also affect prognosis, both the del(11q) and del(17p) are highly significant and play roles in the selection of initial treatment regimens and the treatment in relapsed or refractory patients.

## Conventional Chemotherapy

Although therapeutic options for CLL have evolved over the past several years, the NCCN still recommends that many newly diagnosed patients be enrolled into clinical trials as a first-line treatment option.[8] There are a large number of clinical trials currently ongoing that are evaluating novel drug combinations and new targeted pathways for the treatment of CLL.[8] Where clinical trials are not applicable, first-line chemoimmunotherapy is selected based on Rai stage, ability to tolerate therapy, and presence of either del(11q) or del(17p). For patients with a Rai stage of 0–II who are not eligible for a clinical trial and do not meet other indications for treatment, observation and reevaluation in the future is recommended.[6–8] For patients who initiate therapy, first-line treatment regimens usually consist of a purine analog and an alkylating agent, with or without a CD20-targeting monoclonal antibody.[8] Since the approval of Rituxan® (rituximab) for the treatment of CLL in February 2010, CD20-targeted monoclonal antibodies, in combination with chemotherapeutic agents, have become a popular treatment option for the management of CLL.

Relapsed patients who have had a long duration of response may be retreated with first-line therapy. For patients with a short duration of response (i.e., progression within 24 months) or refractory disease, the regimen should be escalated. For frail refractory patients, the regimen may be a reduced-dose version of a first-line therapy, or a regimen with multiple targeted therapies with the goals of reduced toxicity and increased response. For healthy patients with relapsed or refractory disease, preferred first-line chemoimmunotherapies may remain an option if they have not been previously used; additionally, more intensive chemoimmunotherapy regimens such as RCHOP, R-HyperCVAD, dose-adjusted EPOCH-R, and OFAR may be used, as well as multiple targeted therapies. Enrollment in available clinical trials remains an important aspect of care in the treatment of CLL as new and potentially more effective therapies are being evaluated.[8]

## Recently Approved Novel Therapies

For patients who are unable to tolerate purine analogs, such as frail, elderly patients or those with multiple comorbidities, alternative treatment options now exist.[8] Since receiving FDA approval, Rituxan® has been a mainstay of CLL therapy. Within the last year, however, four novel CLL therapies (Gazyva®, Arzerra®, Imbruvica®, and Zydelig®) have either been approved by the FDA or received an expanded CLL indication. With the availability of these new agents, CLL management approaches are beginning to change.

Based on head-to-head clinical trials demonstrating improved overall survival and progression-free survival (PFS), Gazyva® (obinutuzumab) plus chlorambucil was approved by the FDA in November 2013 and has become an alternative to first-line chemotherapy in patients without mutations.[8] In an open-label, active control, randomized clinical trial, Gazyva®, in combination with chlorambucil, was shown to be superior to chlorambucil monotherapy in previously untreated patients with CLL.[9] The median age of patients enrolled in the study was 73, with 68 percent of patients having a CrCl <70ml/min and 76 percent suffering from multiple coexisting medical conditions.[9] The median PFS in the Gazyva® treatment arm was 26.7 months compared to 11.1 months in patients on chlorambucil monotherapy.[9] This resulted in an overall response rate (ORR) of 77.3 percent for Gazyva® in combination with chlorambucil versus 31.4 percent for the chlorambucil monotherapy arm.[9] The complete response for the Gazyva® treatment arm was 22.3 percent.[9]

Gazyva® is also being studied with various chemotherapy

combinations with preliminary response rates of over 93 percent.[10,14,16] In addition, Gazyva® has been shown to provide greater B-cell depletion and high levels of antitumor activity compared to Rituxan®.[11] In the same trial that compared Gazyva® with chlorambucil monotherapy, Gazyva® was also compared to Rituxan®, both in combination with chlorambucil. The results of this analysis showed a median PFS of 26.7 months in the Gazyva® arm compared to 15.2 months in the Rituxan® arm.[9] The study also showed significant improvement in overall response rates in the Gazyva® arm compared to the Rituxan® arm, 78.4 percent and 65.1 percent respectively, and complete response rates of 20.7 percent and 7 percent respectively.[9] Molecular response was also analyzed, showing significant improvements in the molecular response rates in the Gazyva® arm.[9] The rate of minimal residual disease in bone marrow was 19.5 percent in the Gazyva® treatment arm versus 2.6 percent in the Rituxan® arm.[9] In addition, minimal residual disease measured in the blood was 37.7 percent in the Gazyva® arm compared to 3.3 percent in the Rituxan® arm.[9] With this clinical data, it is not surprising that Gazyva® has largely replaced Rituxan® as the first-line therapy of choice in patients without mutations.

In February 2014, Imbruvica® (ibrutinib), co-marketed by Pharmacyclics and Janssen Biotech, received approval as second-line therapy for the treatment of CLL patients who have received at least one prior therapy.[13] In July 2014, the FDA expanded the indications of Imbruvica® as first-line therapy for CLL patients who carry the del(17p) mutation.[13] Imbruvica® exerts its effect as a Bruton's tyrosine kinase (BTK) inhibitor, which essentially works by blocking the enzyme that allows cancer cells to grow and divide.[13] Results from clinical trials examining the efficacy of Imbruvica® have confirmed the associated benefits.

In one study with 48 patients who were previously treated for CLL, the partial response rate was 58.3 percent. There were no complete responses. The duration of response ranged from 5.6 to greater than 24.2 months (median was not reached).[13]

The accelerated approval from the FDA was based on a randomized study of 391 previously treated patients, of which 127 had CLL with del(17p), in which patients were treated with Arzerra® (ofatumumab) or Imbruvica®. An interim analysis indicated that patients treated with Imbruvica® experienced a 78 percent reduction in risk of disease progression or death (PFS) versus Arzerra®.[13] Data also suggests that Imbruvica®, in addition to having selectively toxic effects on CLL cells, has a unique effect that causes CLL cells to leave the lymph nodes and enter the blood stream. This effect has the potential to further enhance the effectiveness of CD20 antibody therapy, which is currently less effective in bulky/nodal disease.[13–15]

However, these benefits are not without adverse events. The most important is the profound antithrombotic properties associated with Imbruvica®, which were significantly associated with ecchymosis and contusions, and rarely severe bleeding. Bleeding risk is further complicated by the use of anticoagulants and antiplatelet therapy, which are commonly used for many comorbidities in the elderly.[12–14]

In April 2014, the FDA expanded the indication of Arzerra®, in combination with chlorambucil, to include the use in previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.[16] This approval was based on the results of an open-label, randomized trial that compared Arzerra®, in combination with chlorambucil, to chlorambucil monotherapy in previously untreated patients with CLL. The 447 patients enrolled in the study were deemed inappropriate for fludarabine-based therapy due to advanced age (median age of 69 years) or presence of comorbidities (72 percent of patients had two or more comorbidities).[16] The Arzerra® treatment arm was associated with a median PFS of 22.4 months, compared with 13.1 month for patients receiving chlorambucil monotherapy (hazard ratio = 0.57).[16] The results of this study were substantial enough to fulfill the postmarketing requirements for GlaxoSmithKline (manufacturer of Arzerra®) to verify the clinical benefit of Arzerra®.[16]

In July 2014, the FDA approved Zydelig® (idelalisib), manufactured by Gilead Sciences, Inc., in combination with Rituxan®, for the treatment of patients with relapsed CLL.[17] The approval in CLL is supported primarily by data from a randomized, placebo-controlled phase 3 trial of Zydelig® plus Rituxan® in 220 patients with relapsed CLL who were not able to tolerate standard chemotherapy due to coexisting medical conditions.[17] The median number of prior therapies was three, of which 96 percent of patients had received prior anti-CD20 monoclonal antibodies.[17] The study was stopped early because it showed significant benefit in PFS in the Zydelig® arm as compared to those receiving Rituxan® alone (hazard ratio = 0.18, $p<0.0001$). Median PFS was not reached in the Zydelig plus Rituxan® arm.[17]

The safety and efficacy data derived from these agents may one day help replace the harsher chemotherapy agents used to treat CLL. With the emergence of biologic treatment options, patients may be able to tolerate therapy for longer durations of time, because the side effects are much more tolerable than conventional chemotherapy. These agents allow for the targeted destruction of cancerous CLL cells, while leaving the healthy cells intact. With further study, it is

likely that these novel products will expand into earlier treatment settings and possibly for other types of cancer.

## Managed Care Implications

CLL is a rare disorder that, like most hematologic malignancies, has been associated with poor response rates and survival. To further complicate treatment, many patients with CLL are elderly and present with comorbidities that can limit treatment all the more. The mainstays of treatment have conventionally been limited to chemotherapy or immunotherapy, with highly variable efficacy. Furthermore, a scarcity of therapies for heavily pretreated or refractory patients leaves a large gap in treatment options.

Emerging therapies help to fill these gaps. With the advent of improved monoclonal antibodies (Gazyva® and Arzerra®) and novel kinase modulation (Imbruvica® and Zydelig®), there exists an opportunity to improve health outcomes. As it stands, these four novel therapies have demonstrated improved efficacy in late-stage trials. As more novel agents emerge, it is important for managed care organizations to analyze both the clinical and economic impact that these products can have on their patient population, with a specific focus on tolerability and side effect profiles.

These newer agents are expensive, with maintenance therapy ranging from $4,704/month for Arzerra® in previously untreated patients to $9,408/month for Arzerra® in refractory patients. This is in line with the cost for agents to treat solid tumors. Nevertheless, novel therapies in the treatment of CLL present exciting treatment advances. As more studies are done comparing new agents head-to-head and in combination with other novel therapies, it can be expected that even more effective regimens will be identified for this highly variable disease. While the current spectrum of these novel treatments is still young, managed care organizations have an opportunity to improve quality of care for patients by focusing on optimizing utilization of new agents through appropriate patient identification. As more effective therapies come to market, the current CLL treatment paradigm is likely to change drastically and, hopefully, result in better response rates, fewer adverse events, and better overall survival for patients suffering from this condition.

**Brief Overview of Recently Approved Products for the Treatment of CLL[9,10,13,17,19]**

| | Gazyva® (obinutuzumab) | Arzerra® (ofatumumab) | Imbruvica® (ibrutinib) | Zydelig® (idelalisib) |
|---|---|---|---|---|
| Manufacturer | Genentech, Inc. | GlaxoSmithKline | Janssen / Pharmacyclics | Gilead |
| Class | CD20-targeted monoclonal antibody | CD20-directed cytolytic monoclonal antibody | Bruton's tyrosine kinase (BTK) inhibitor | Phosphatidylinositol 3-kinase (PI3Kδ) inhibitor |
| Indications | • Treatment of patients with previously untreated CLL in combination with chlorambucil | • In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate<br>• For the treatment of patients with CLL refractory to fludarabine and alemtuzumab | • Treatment of patients with CLL who have received at least one prior therapy<br>• Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy<br>• Treatment of patients with CLL who carry a deletion in chromosome 17 (17p deletion) | • Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities<br>• Relapsed follicular B-cell non-Hodgkin's lymphoma in patients who have received at least two prior systemic therapies<br>• Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies |
| Dosing for CLL Indication | First cycle, Gazyva® 100 mg, administered intravenously, on day 1, followed by 900 mg on day 2, then 1,000 mg on days 8 and 15; Cycles 2 to 6 (28 days each), Gazyva® 1,000 mg on day 1 | Previously untreated patients:<br>• 300 mg on day 1 followed by 1,000 mg on day 8 (cycle 1)<br>• 1,000 mg on day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best response or a maximum of 12 cycles<br>Refractory CLL:<br>• 300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses | 420 mg (three 140 mg capsules) once daily | 150 mg twice daily |

## Price Comparison of the New Agents for CLL Management[19]

| | Cycle 1 (28 days) | Cycles 2-6 (every 28 days) |
|---|---|---|
| Gazyva® | $15,480 | $5,160 |

| | Cycle 1 (28 days) | Subsequent Cycles (maximum of 12 cycles) |
|---|---|---|
| Arzerra® (previously untreated) | $6,116 | $4,704 |

| | Month 1 | Month 2 | Months 3-6 |
|---|---|---|---|
| Arzerra® (refractory) | $29,637 | $37,634 | $9,409 |

| | Monthly Cost |
|---|---|
| Imbruvica® | $8,200 |
| Zydelig® | $7,200* |

*Pricing does not include cost associated with Rituxan® therapy per product indication.

## Efficacy Results from Randomized Clinical Trials[9,10,13,16,17]

| Gazyva®/Chlorambucil versus Chlorambucil: Studied in previously untreated CLL patients | | |
|---|---|---|
| | Gazyva® + chlorambucil (N=238) | Chlorambucil (N=118) |
| Median Progression-Free Survival | 26.7 months | 11.1 months |
| | Hazard Ratio = 0.18 | |
| Overall Survival | Hazard Ratio = 0.41 | |
| Overall Response Rate | 77.3% | 31.4% |
| Complete Response | 22.3% | |

| Rituxan®/Chlorambucil versus Chlorambucil: Studied in previously untreated CLL patients | | |
|---|---|---|
| | Rituxan® + chlorambucil (N=233) | Chlorambucil (N=118) |
| Median Progression-Free Survival | 16.3 months | 11.1 months |
| | Hazard Ratio = 0.44 | |
| Overall Survival | Hazard Ratio = 0.66 | |
| Overall Response Rate | 65.7% | 31.4% |
| Complete Response | 7.3% | |

| Gazyva®/Chlorambucil versus Rituxan®/Chlorambucil: Studied in previously untreated CLL patients | | |
|---|---|---|
| | Gazyva® + chlorambucil (N=333) | Rituxan® + chlorambucil (N=329) |
| Median Progression-Free Survival | 26.7 months | 15.2 months |
| | Hazard Ratio = 0.39 | |
| Overall Response Rate | 78.4% | 65.1% |
| Complete Response | 20.7% | 7% |

| Arzerra®/Chlorambucil versus Chlorambucil: Studied in previously untreated CLL patients | | |
|---|---|---|
| | **Arzerra® + chlorambucil (N=221)** | **Chlorambucil (N=226)** |
| Median Progression-Free Survival | 22.4 months | 13.1 months |
| | Hazard Ratio = 0.57 | |
| Overall Response Rate | 82% | 69% |
| Complete Response | 12% | 1% |

| Imbruvica® versus Arzerra®: Studied in previously treated CLL patients | | |
|---|---|---|
| | **Imbruvica® (N = 195)** | **Arzerra® (N = 196)** |
| Median Progression-Free Survival | Not reached | 8.1 months |
| | Hazard Ratio = 0.22 | |
| Overall Survival* | Hazard Ratio = 0.43 | |
| Overall Response Rate** | 42.6% | 4.1% |

*Median OS not reached for either arm.

**IRC evaluated. All responses were partial responses; none of the patients achieved a complete response.

| Zydelig®/Rituxan® versus Placebo/Rituxan®: Studied in patients with relapsed CLL who were not able to tolerate standard chemotherapy | | |
|---|---|---|
| | **Zydelig® + Rituxan® (N = 110)** | **Placebo + Rituxan® (N = 110)** |
| Median Progression-Free Survival* | Not reached | 5.5 months |
| | Hazard Ratio = 0.18 | |
| | P-value <0.0001 | |

* Idelalisib trial was stopped for efficacy following the first pre-specified interim analysis.

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# Impact of New Therapies on the Management of Metastatic Melanoma

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Melanoma is one of the most dangerous and fastest-growing types of cancer.[1] Although melanoma is easier to detect in localized stages when compared with most other cancers, because of the aggressive nature of the disease, it is highly likely to metastasize to other parts of the body. This makes early identification essential to optimize survival outcomes. Melanoma is almost always curable when it is detected in early stages and treated accordingly. However, if left untreated, it can spread very rapidly to other parts of the body and patient survival is greatly reduced. The five-year survival rate for localized stage I and II melanoma is 98 percent; however, the five-year survival rate decreases significantly, to 16 percent, in cases where melanoma has metastasized to distant sites or organs.[1]

Until 2011, only two treatments for metastatic melanoma, dacarbazine and high-dose interleukin 2 (HD IL-2), were approved by the FDA.[2] Both treatments were limited due to a low response rate, low overall survival rate, and severe toxicity, with only a minority of patients achieving a "long-term, durable response."[2] It became clear that there needed to be a major focus on drug development in order to improve the response rates and duration of response associated with treatment options available for metastatic melanoma.

Recognition of key molecular mutations that drive the formation of tumors in melanoma has led to the development of promising treatments that selectively target and inhibit tumor growth, ultimately providing improved response rates and decreased toxicity.[2] In addition, advancements in our understanding of melanoma immunotherapy have led to new agents that are less toxic and have demonstrated improved long-term health benefits. However, limitations still remain and promising future therapies are in development to overcome these clinical barriers.

## Targeted Therapies for Melanoma Treatment

In 2011, the FDA approved two promising therapies for the treatment of advanced melanoma, vemurafenib (Zelboraf®) and ipilimumab (Yervoy®). The development of these two agents provided optimism for

physicians and patients with metastatic melanoma; however, the limitations associated with each therapy further emphasize the importance of developing other treatment strategies to improve response rates and duration of response. While Zelboraf® provided a major breakthrough in the treatment of melanoma, resistance to therapy invariably develops, with the median duration of benefit being approximately six months.[2] On the contrary, Yervoy® is capable of inducing long-term responses in a minority of patients, but the relatively low response rate (10 to 15 percent) and meager improvement in median survival (two months) limit its utility.[2]

In 2014, the FDA approved the combination therapy of dabrafenib (Tafinlar®), a BRAF inhibitor, and trametinib (Mekinist™), a mitogen-activated protein kinase (MEK) inhibitor. Data had indicated that, with the combination of BRAF and MEK inhibitors, the response rate is higher compared with using each therapy separately, ranging from 80 to 90 percent.[3] In addition, the drug toxicity appears to be improved when the BRAF and MEK inhibitors are combined versus when they are given alone. Unfortunately, the number of patients with complete response to targeted therapies still remains low.

## Future of Immunotherapy

New immunotherapies may hold the highest expectations and optimism for melanoma treatment. Along with the recently approved therapies that have demonstrated superior efficacy, there are more drugs that are currently under development with some encouraging results. New targeted treatments focus on blocking either the programmed cell death 1 (PD-1) or programmed death-ligand 1 (PD-L1) protein, potentially boosting the ability of the immune system to fight cancer.[4] Antoni Ribas, MD, PhD, Professor of Medicine at the UCLA Jonsson Comprehensive Cancer Center in Los Angeles, explained, "Basically, the cancer cells throw up a stop sign, which is obeyed by anticancer cells; pembrolizumab and other PD-1 inhibitors remove that stop signal, allowing the immune system cells to attack the tumor."[5] These inhibitors have been shown to produce high and long-lasting response rates.

Bristol-Myers Squibb (BMS) has been investigating nivolumab, a PD-1 being studied in late-stage clinical trials. BMS recently announced the results of a phase 3 study comparing nivolumab versus dacarbazine in patients with previously untreated BRAF wild-type advanced melanoma. The study was stopped early because an analysis showed evidence of superior overall survival in patients receiving nivolumab.[6] Another study demonstrated that nivolumab in combination with Yervoy® led to rapid and lasting tumor shrinkage in up to 50 percent of patients with advanced melanoma, as well as a two-year survival rate of 79 percent.[7] These findings suggest that the combination of these two therapies would be clinically meaningful in first-line treatments for patients with advanced melanoma.

Another PD-1 inhibitor, pembrolizumab, under development by Merck, is challenging nivolumab in the race to become the first FDA-approved PD-1 inhibitor. A study revealed that pembrolizumab produced responses in 34 percent of patients, including 28 percent of patients whose disease progressed on prior treatment with Yervoy®.[8] Also, pembrolizumab displayed a very favorable toxicity profile. The most common adverse events of any grade were fatigue, pruritus, and rash, but none of these, including other reported adverse events, affected more than 1 to 2 percent of patients. These results have won a breakthrough therapy designation by the FDA and also a priority review designation under the accelerated approval program.[8] Steven O'Day, MD, Clinical Professor of Medicine at the University of Southern California, stated, "The remarkable thing is that almost 90 percent of these patients are having durable responses with a toxicity profile that is almost unheard of in metastatic cancer—10 or 12 percent. This is really extraordinary about this class of drugs."[8]

Both nivolumab and pembrolizumab show promising results and may provide a positive opportunity for patients with metastatic melanoma in the near future. Based on the currently available results, small differences in efficacy and toxicity profiles between these products may make a substantial impact on overall market dynamics. Once these products become commercially available, it will be interesting to see the associated impact on product sequencing and combination therapy. Many physicians feel that these products will have a profound impact on the overall management strategy in the treatment of advanced melanoma.[3]

## Future Managed Care Implications

As new pharmacologic agents become available, it is important to understand the full spectrum of treatments that are currently available, and how these products are likely to impact physician decision making and overall patient outcomes. Over the next year, the melanoma

treatment landscape will evolve based on the availability of new products. It is entirely possible that these alternative therapies could modify the current sequencing of both pharmacologic therapy and surgical options. However, the impact that these products will have on therapeutic sequencing remains unknown. Additionally, the duration of therapy is still largely in question.

One could argue that the advent of new therapeutic agents generates more questions than are answered in the controlled trials leading to drug approval. Central to answering the questions of sequencing and duration of therapy is the availability of longer-term post-marketing data on drug and disease performance over time in uncontrolled settings. Today, there is not a universally agreed upon "evidence base" for many therapeutic decisions in this space. Many physicians are still trying to determine whether to continue pharmacologic therapy if surgery is performed and the patient is considered disease-free. As more data becomes available, it will hopefully become clearer to physicians how to appropriately manage patients with pharmacotherapy. The goal of immunotherapy is to prolong survival and quality of life for melanoma patients, and PD-1 inhibitors will most likely impact future strategies in the management of metastatic melanoma.

Although the most important pharmacologic considerations made when reviewing oncology products should always be safety and efficacy, the influence these agents will have on healthcare resources is always an area of concern. Managed care organizations are continually tasked with appropriately managing their financial resources, and new pharmacologic agents are often associated with an increased cost burden. The primary goal is to provide access to the most therapeutically appropriate products that have the potential to improve overall outcome, while simultaneously controlling the continually escalating healthcare expenditure. For many years, the pharmacoeconomic impact of oncology disease states was somewhat overlooked. However, with the addition of multiple market entrants, managed care organizations now have the ability to analyze potential opportunities for cost-savings in the oncology arena. New products used to treat metastatic melanoma will most likely be expensive and managed care organizations will need to assess whether newly approved pharmaceuticals will be cost-effective treatment options.

As the U.S. population is steadily aging, the health and economic concerns associated with metastatic melanoma will only progress with time. New and novel therapeutic alternatives should be researched with the goal of extending survival, limiting the need for chemotherapy, improving quality of life, and reducing unnecessary adverse reactions. Pharmaceutical products that are able to achieve these goals will enhance the quality of care offered to patients with metastatic melanoma and ensure the maximum health and survival benefits are obtained. With the approval of new pharmacologic agents, it is important to continually assess the current treatment modalities and determine when modifications should be made. Additional agents also highlight the need for a more structured management approach to ensure value in achieving positive outcomes.

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# Real-World Analysis of the Economic Impact of Infliximab Utilization by Site of Care and Medical Diagnosis Within Two Regional Health Plans

Infusion management has ascended to the forefront of payor concerns in recent years, due largely to the high percentage of costs of total drug spend. Total annual spend on medical pharmacy injectable drugs per million lives has been estimated to be approximately $250 million and has been rising steadily in recent years.[1] Excessive cost associated with certain sites of care (SOC) for medical infusions has emerged as a significant issue due to misaligned incentives related to pharmacy/medical benefit design, expansion of 340B-covered entities, decreased drug reimbursement to office-based physicians, and lack of awareness by providers of alternative options. Past research has demonstrated consistently higher costs per claim of medical benefit specialty drugs at hospital outpatient facilities (HOPs) compared with alternative SOC.[2,3]

Infliximab is used to treat a large variety of disease states, with annual costs per million lives of approximately $21 million.[1,4] Currently, there is limited understanding of the economic impact that medical diagnosis has on infliximab utilization within various SOC. Health plans interested in implementing a site of care optimization program may find this data useful to assist in targeting such an initiative on a specific subset of patients.

The objective of this analysis was to identify how utilization of infliximab differs by SOC and disease categories, and the impact this has on financial expenditures. To do so, medical claims databases from two regional health plans were utilized, containing approximately 4 million lives. All continuously enrolled health plan patients who were administered infliximab between January 1, 2013 and December 31, 2013 were identified. Medical diagnosis, SOC, infliximab utilization data, and cost were identified for each claim. Diagnoses were grouped into the following categories: rheumatoid/musculoskeletal conditions; gastrointestinal (GI) conditions; dermatologic conditions; ocular inflammatory conditions; oncology/hematology conditions; and other.

A total of 3,161 unique patients were administered infliximab therapy, representing 17,903 total claims and $88,032,179 in cost. Of the 17,903 claims, 6.5 percent were administered through home infusion and/or specialty pharmacy (HI/SP), with an average paid amount per claim of $4,293; 34.3 percent were administered in a HOP, with an average paid amount of $7,302 per claim; and 59.1 percent were administered in a physician office, with an average paid amount of $3,606 per claim.

The total spend per disease category was $48,360,142 for GI conditions, with $32,515,633 (67 percent), $12,821,810 (27 percent), and $2,995,893 (6 percent) being accounted for by HOPs, physician offices, and HI/SP,

respectively, and $35,096,887 for rheumatoid/musculoskeletal conditions, with $9,177,723 (26 percent), $24,140,500 (69 percent), and $1,778,664 (5 percent) being accounted for by HOPs, physician offices, and HI/SP, respectively. The total spend for all other disease groups was less than $5 million. The average units per claim were 41.4 units in the HOPs compared with 49.7 units in physician offices. The units per claim for gastrointestinal conditions were 26 percent higher in physician offices compared with HOPs, but only 12 percent higher in physician offices compared with HOPs for rheumatoid/musculoskeletal conditions.

This analysis demonstrated that choice of SOC for infusions can be associated with a high degree of unnecessary costs. The average claim cost from a HOP was 102 percent higher than the average claim cost from a physician office, even though the average units per claim in the physician offices were 20 percent higher. Additionally, SOC utilization differs dramatically according to disease state. Approximately 67 percent of all infliximab spend for GI conditions is billed from HOPs, compared with just 26 percent for rheumatoid/musculoskeletal conditions.

It is important to remember that costs associated with SOC are not unique to infliximab. This analysis used infliximab as an example, but similar challenges exist for many other infused products, especially in the oncology space. Before implementing a site of care initiative, it is critical to conduct a comprehensive evaluation of utilization data to identify disease categories with a high percentage of HOP utilization. This is one opportunity for managed care organizations to reduce unnecessary utilization and target specific patient populations when evaluating SOC cost containment strategies.

**Table 1 Infliximab Medical Claims Breakdown by Site of Service**

| Place of Service | Allowed Amount | ASP | Number of Units | Number of Claims | Number of Members | ASP + | Average Units/Claim | Average Paid Amount/Claim |
|---|---|---|---|---|---|---|---|---|
| Home Infusion/Specialty Pharmacy | $5,027,543 | $4,020,941 | 60,793 | 1,171 | 231 | 25.03% | 51.9 | $4,293 |
| Hospital Outpatient | $44,792,669 | $16,781,887 | 253,727 | 6,134 | 1,222 | 166.91% | 41.4 | $7,302 |
| Physician Office | $38,181,910 | $34,794,204 | 526,057 | 10,588 | 1,924 | 9.74% | 49.7 | $3,606 |
| **Grand Total** | **$88,032,179** | **$55,631,954** | **841,105** | **17,903** | **3,381** | **58.24%** | **47.0** | **$4,917** |

**Figure 1: Infliximab Spend According to SOC and Diagnosis**

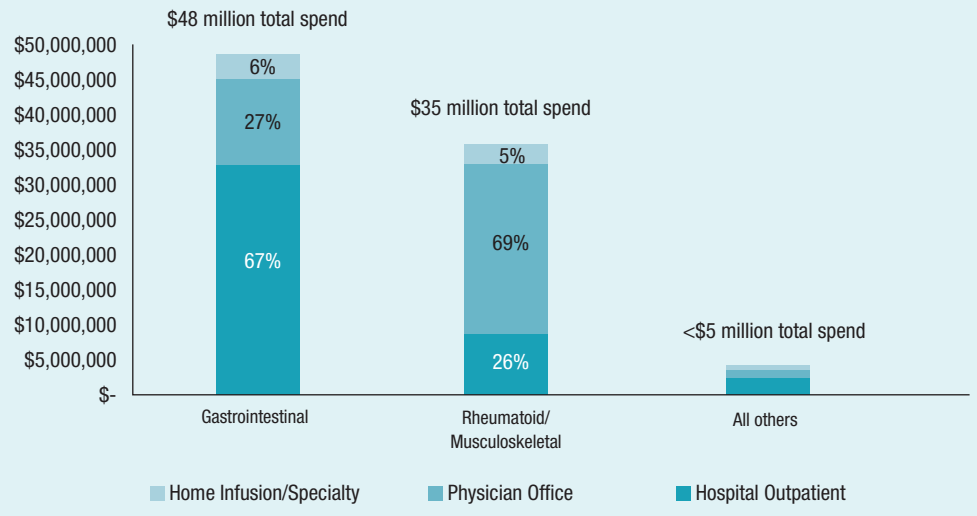

**Table 2** **Infliximab Medical Claims Breakdown by Diagnosis**

| Disease Group | SOC | Allowed Amount | Number of Units | Number of Claims | Average Units/Claim | Average Paid Amount/Claim |
|---|---|---|---|---|---|---|
| Gastrointestinal | HOSPITAL OP | $32,515,633 | 170,448 | 4,252 | 40.09 | $7,647 |
| | PHYSICIAN | $12,821,810 | 176,335 | 3,488 | 50.55 | $3,676 |
| | HI/SPP | $2,995,893 | 35,668 | 729 | 48.93 | $4,110 |
| | Total | $48,360,142 | 382,686 | 8,475 | 45.15 | $5,706 |
| Rheumatoid/ Musculoskeletal | PHYSICIAN | $24,140,500 | 333,493 | 6,811 | 48.96 | $3,544 |
| | HOSPITAL OP | $9,177,723 | 64,872 | 1,490 | 43.54 | $6,160 |
| | HI/SPP | $1,778,664 | 22,081 | 398 | 55.48 | $4,469 |
| | Total | $35,096,887 | 420,446 | 8,699 | 48.33 | $4,035 |
| Dermatologic | PHYSICIAN | $846,730 | 10,794 | 186 | 58.03 | $4,552 |
| | HOSPITAL OP | $717,001 | 3,724 | 72 | 51.72 | $9,958 |
| | HI/SPP | $128,515 | 1,544 | 29 | 53.24 | $4,432 |
| | Total | $1,692,246 | 16,062 | 287 | 55.97 | $5,896 |
| Other | HOSPITAL OP | $1,124,456 | 6,745 | 152 | 44.38 | $7,398 |
| | PHYSICIAN | $202,666 | 3,035 | 58 | 52.33 | $3,494 |
| | HI/SPP | $72,749 | 870 | 8 | 108.75 | $9,094 |
| | Total | $1,402,879 | 10,924 | 221 | 49.43 | $6,348 |
| Ocular Inflammatory | HOSPITAL OP | $635,177 | 3,181 | 69 | 46.10 | $9,205 |
| | PHYSICIAN | $97,078 | 1,340 | 25 | 53.60 | $3,883 |
| | HI/SPP | $51,722 | 630 | 7 | 90.00 | $7,389 |
| | Total | $783,977 | 5,151 | 101 | 51.00 | $7,762 |
| Oncology/Hematology | HOSPITAL OP | $622,678 | 4,757 | 99 | 48.05 | $6,290 |
| | PHYSICIAN | $73,125 | 1,060 | 20 | 53.00 | $3,656 |
| | Total | $696,047 | 5,836 | 120 | 48.63 | $5,800 |
| **Grand Total** | | **$88,032,179** | **841,105** | **17,903** | **46.98** | **$4,917** |

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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.**

- **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.**

### IMPORTANT SAFETY INFORMATION

**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. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).
- **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:** The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs placebo, respectively, was:

- Akathisia (8% vs 4%) in adult patients with schizophrenia.

**Injection Site Reactions:** In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena-treated patients.

**Dystonia** is a class effect of antipsychotic drugs. 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 excreted 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 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. 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.

**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. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving ABILIFY MAINTENA as well.

- **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 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 an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 1 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

**Table 1: Changes in Fasting Glucose From Placebo-controlled Monotherapy Trials in Adult Patients**

| | Category Change (at least once) from Baseline | Treatment Arm | n/N | % |
|---|---|---|---|---|
| **Fasting Glucose** | Normal to High (<100 mg/dL to ≥126 mg/dL) | Aripiprazole | 31/822 | 3.8 |
| | | Placebo | 22/605 | 3.6 |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Aripiprazole | 31/176 | 17.6 |
| | | Placebo | 13/142 | 9.2 |

  At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

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

  There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

  Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

**Table 2: Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults**

| | Treatment Arm | n/N | % |
|---|---|---|---|
| **Total Cholesterol** | Aripiprazole | 34/1357 | 2.5 |
| Normal to High (<200 mg/dL to ≥240 mg/dL) | Placebo | 27/973 | 2.8 |
| **Fasting Triglycerides** | Aripiprazole | 40/539 | 7.4 |
| Normal to High (<150 mg/dL to ≥200 mg/dL) | Placebo | 30/431 | 7.0 |
| **Fasting LDL Cholesterol** | Aripiprazole | 2/332 | 0.6 |
| Normal to High (<100 mg/dL to ≥160 mg/dL) | Placebo | 2/268 | 0.7 |
| **HDL Cholesterol** | Aripiprazole | 121/1066 | 11.4 |
| Normal to Low (≥40 mg/dL to <40 mg/dL) | Placebo | 99/794 | 12.5 |

  In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/ nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

  Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

**Table 3: Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight**

| | Indication | Treatment Arm | N | n (%) |
|---|---|---|---|---|
| **Weight gain ≥7% of body weight** | Schizophrenia[a] | Aripiprazole | 852 | 69 (8.1) |
| | | Placebo | 379 | 12 (3.2) |
| | Bipolar Mania[b] | Aripiprazole | 719 | 16 (2.2) |
| | | Placebo | 598 | 16 (2.7) |

[a]4-6 weeks' duration. [b]3 weeks' duration.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its $\alpha_1$-adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with ABILIFY MAINTENA during the stabilization phase, 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 stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) was 0.2% (1/575).

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC 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 in the *Full Prescribing Information:*

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.9)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*

**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:** 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 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult patients in clinical trials in schizophrenia, with approximately 1,281 patient-years of exposure to ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 630 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 profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. Therefore, most of the safety data presented below are derived from trials with the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections under double-blind conditions, the incidence of adverse reactions was similar between the two treatment groups.

**Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole:** *Adverse Reactions Associated with Discontinuation of Oral Aripiprazole:* Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the incidence of discontinuation due to adverse reactions was 7% in oral aripiprazole-treated and 9% in placebo-treated patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

*Commonly Observed Adverse Reactions of Oral Aripiprazole:* Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the only commonly observed adverse reaction associated with the use of oral aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

*Less Common Adverse Reactions in Adults Treated with Oral Aripiprazole:* Table 4 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with oral aripiprazole (doses ≥2 mg/ day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

**Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients Treated with Oral Aripiprazole**

| | Percentage of Patients Reporting Reaction[a] | |
|---|---|---|
| **System Organ Class Preferred Term** | **Oral Aripiprazole (n=1843)** | **Placebo (n=1166)** |
| **Eye Disorders** | | |
| Blurred Vision | 3 | 1 |
| **Gastrointestinal Disorders** | | |
| Nausea | 15 | 11 |
| Constipation | 11 | 7 |
| Vomiting | 11 | 6 |
| Dyspepsia | 9 | 7 |
| Dry Mouth | 5 | 4 |
| Toothache | 4 | 3 |
| Abdominal Discomfort | 3 | 2 |
| Stomach Discomfort | 3 | 2 |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 6 | 4 |
| Pain | 3 | 2 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Musculoskeletal Stiffness | 4 | 3 |
| Pain in Extremity | 4 | 2 |
| Myalgia | 2 | 1 |
| Muscle Spasms | 2 | 1 |
| **Nervous System Disorders** | | |
| Headache | 27 | 23 |
| Dizziness | 10 | 7 |
| Akathisia | 10 | 4 |
| Sedation | 7 | 4 |
| Extrapyramidal Disorder | 5 | 3 |
| Tremor | 5 | 3 |
| Somnolence | 5 | 3 |
| **Psychiatric Disorders** | | |
| Agitation | 19 | 17 |
| Insomnia | 18 | 13 |
| Anxiety | 17 | 13 |
| Restlessness | 5 | 3 |
| **Respiratory, Thoracic, and Mediastinal Disorders** | | |
| Pharyngolaryngeal Pain | 3 | 2 |
| Cough | 3 | 2 |

[a]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

*Dose-Related Adverse Reactions of Oral Aripiprazole:* Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

*Injection Site Reactions of ABILIFY MAINTENA:* In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the first to the last injection in the open-label, stabilization phase (6.1 to 4.9).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent for 74%-96% of subjects following the first injection and 77%-96% of subjects following the last injection.

*Extrapyramidal Symptoms of Oral Aripiprazole:* In short-term, placebo-controlled trials in schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, –0.05).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias) did not show a difference between aripiprazole and placebo.

*Dystonia: Class Effect:* 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.

*Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials of Oral Aripiprazole:* The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for oral aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (40/859) for oral aripiprazole.

*Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole:* Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6),* or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

*Blood and Lymphatic System Disorders:* ≥1/1000 patients and <1/100 patients - thrombocytopenia; Cardiac Disorders: ≥1/1000 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia; <1/1000 patients - atrial flutter, supraventricular tachycardia, ventricular tachycardia; *Eye Disorders:* ≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia; *Gastrointestinal Disorders:* ≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; <1/1000 patients - pancreatitis; *General Disorders and Administration Site Conditions:* ≥1/100 patients - asthenia, peripheral edema, chest pain; ≥1/1000 patients and <1/100 patients - face edema, angioedema; <1/1000 patients - hypothermia; *Hepatobiliary Disorders:* <1/1000 patients - hepatitis, jaundice; *Immune System Disorders:* ≥1/1000 patients and <1/100 patients - hypersensitivity; *Injury, Poisoning, and Procedural Complications:* ≥1/100 patients - fall; <1/1000 patients - heat stroke; Investigations: ≥1/1000 patients and <1/100 patients - blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased; <1/1000 patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased; *Metabolism and Nutrition Disorders:* ≥1/1000 patients and <1/100 patients - anorexia, hyponatremia, hypoglycemia, polydipsia; <1/1000 patients - diabetic ketoacidosis; *Musculoskeletal and Connective Tissue Disorders:* ≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; <1/1000 patients - rhabdomyolysis; *Nervous System Disorders:* ≥1/100 patients - coordination abnormal; ≥1/1000 patients and <1/100 patients - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; <1/1000 patients - choreoathetosis; *Psychiatric Disorders:* ≥1/100 patients - suicidal ideation; ≥1/1000 patients and <1/100 patients - loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; <1/1000 patients - catatonia, sleepwalking; *Renal and Urinary Disorders:* ≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; <1/1000 patients - gynecomastia, priapism; *Respiratory, Thoracic, and Mediastinal Disorders:* ≥1/100 patients - nasal congestion, dyspnea; *Skin and Subcutaneous Tissue Disorders:* ≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥1/1000 patients and <1/100 patients - pruritus, photosensitivity reaction, alopecia, urticaria.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of oral aripiprazole. 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: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm).

**DRUG INTERACTIONS: Carbamazepine or Other CYP3A4 Inducers:** Concomitant use of ABILIFY MAINTENA with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days *[see Indications and Usage, Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].*

**Ketoconazole or Other Strong CYP3A4 Inhibitors:** Concomitant use of ABILIFY MAINTENA with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

**Quinidine or Other Strong CYP2D6 Inhibitors:** Concomitant use of ABILIFY MAINTENA with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of quinidine or other CYP2D6 inhibitors with ABILIFY MAINTENA does not require a dose adjustment.

**CNS Depressants:** Given the CNS depressant effects of aripiprazole, use caution when ABILIFY MAINTENA is taken in combination with other centrally-acting drugs or alcohol.

**Anti-Hypertensive Agents:** Due to its $\alpha_1$-adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** *Pregnancy Category C: Risk Summary:* Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1-10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m$^2$ body surface area. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data: Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m$^2$ body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30 mg/day based on mg/m$^2$ body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/ kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m$^2$ body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m$^2$ body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

**Nursing Mothers:** Aripiprazole is excreted 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.

**Pediatric Use:** Safety and effectiveness of ABILIFY MAINTENA in patients <18 years of age have not been evaluated.

**Geriatric Use:** Safety and effectiveness of ABILIFY MAINTENA in patients >60 years of age have not been evaluated. In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment of ABILIFY MAINTENA is recommended for elderly patients *[see also Boxed Warning and Warnings and Precautions (5.1)].*

**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 *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].*

**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.

**PATIENT COUNSELING INFORMATION:** Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ABILIFY MAINTENA.

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# Biosimilar Update: FDA Guidance, First Accepted Application, 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, there are still several unanswered questions regarding the biosimilar approval process. 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 entitled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," which is more specifically directed towards 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 also outlines the pharmacokinetic (PK) and pharmacodynamic (PD) data required to support biosimilarity between the biological product and the reference product.[2] The document's introduction states that, "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 to be seen, as this guidance is one in a series 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:

- Exposure and Response Assessment
- Evaluation of Residual Uncertainty
- Assumptions about Analytical Quality and Similarity

The draft discusses four different assessment categories, and states that "the result of the comparative analytical characterization may lead to one of the four assessments within a development-phase continuum."[2] 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 that are extremely sensitive in identifying analytical differences."[2] These drugs would require "targeted and 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 if the product is highly similar to the reference product. Additional analytical data or other studies are necessary to determine if 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]

On August 4, 2014, the FDA released a draft guidance entitled "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.[3] 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, it cannot be approved by the FDA until 12 years after the date the reference product was first referred to in the biosimilar application approval pathway.[3] The reference product exclusivity period is defined as the period of time the product cannot be licensed or submitted for review.[3] 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.[3]

Lastly, 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.[3] This includes:

- A list of all licensed biological products that are structurally related to the biological product that is subject to the 351(a) application being considered[3]
- A list of those biological products listed above 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[3]
- A description of structural differences between those products and the BLA product under consideration[3]
- Evidence of the change in safety, purity, and/or potency between those products and the BLA product under consideration[3]

## First Biosimilar Application Accepted by the FDA

In July 2014, Sandoz, a Novartis subsidiary, announced that 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 towards making high-quality biologics more accessible in the U.S., and we applaud the 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

In regard to indications, the barrier still remains as to whether all the indications of the reference product will be connected to the biosimilar, since there may not be clinical evidence to support each indication.

increase U.S. patient access to affordable, high-quality biologics, while reducing the financial burden on payors 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 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, which is more than any other drug manufacturer, making Sandoz the pioneer and global leader in the biosimilars market.[4]

If the drug is approved, this could be used to gauge how drug manufacturers will price their products relative to reference products.[5] After the passage of the BPCI Act, many had forecasted that, as Alexander Gaffney, RAC, of the Regulatory Affairs Professionals Society wrote, "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.[5]

## Challenges Still Remain

The new guidance did not add any comment as to how the biological product could be interchangeable with the reference product. The FDA still feels that it is arduous for the biosimilar to establish interchangeability with the reference product. Although the FDA did provide some guidance as to what drug manufacturers need to do in order to submit for the approval of the proposed biosimilar, individuals are still anxiously awaiting approval of the process. The most substantial challenges still remain with indications, substitution, and physician and patient uptake. In regard to indications, the barrier still remains as to whether all the indications of the reference product will be connected to the biosimilar, since there may not be clinical evidence to support each indication. Applying safety and efficacy data across all indications can pose difficulties, and may be inappropriate for biosimilars without relying on strong scientific data due to the variation of the data and how it pertains to the different indications. This will impact the ability to optimize the savings potential associated with biosimilar products.

Substitution remains an issue because there is still ambiguity surrounding whether or not pharmacists will be allowed to substitute a biosimilar for a biologic without physician approval. The Affordable Care Act allows interchangeable biosimilars to be substituted for the reference product without healthcare provider approval, but it's up to each state to decide if it will allow such substitutions. Additionally, the FDA has stated that, "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."[6] Therefore, automatic substitution by pharmacists might eventually be an irrelevant conversation.

If Sandoz's biologic is approved, the drug will be subject to a highly debated issue as to what the drug should be called. While there are two schools of thought with regard to this issue, many branded biologic entities feel there should be distinctive generic names for the drugs, saying 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 the patients to think that the drug is not as safe or effective as the original.[5]

Lastly, manufacturers of biosimilars in the United States will have to overcome the challenge of educating providers regarding biosimilars, and develop strategies to ease the physician's concerns and overcome the reluctance to utilize the new products. Biosimilars will have to be marketed similar to branded agents, which may also impact the overall cost-savings potential associated with these products.

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NEW PHASE 3 DATA

# IMBRUVICA® demonstrated single-agent survival in previously treated CLL

**INDICATIONS:** IMBRUVICA® is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of patients with:

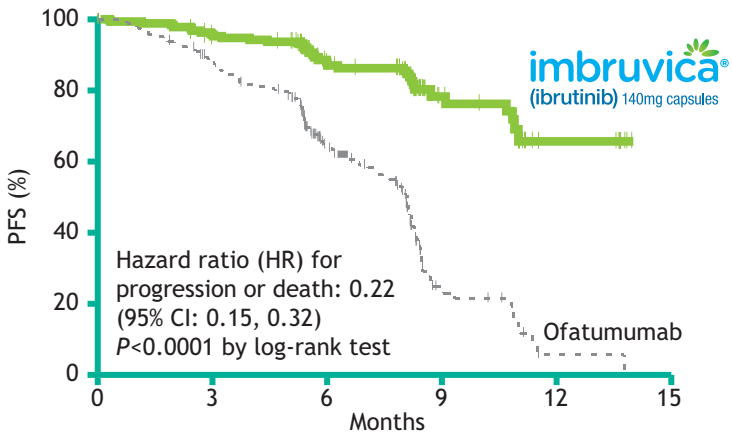
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- CLL with 17p deletion

## Significantly improved overall survival (OS)—secondary endpoint

- 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA® arm (HR=0.43; 95% CI: 0.24, 0.79)
- Median OS not yet reached in either treatment arm
- 29% of ofatumumab patients crossed over to receive IMBRUVICA® upon progression

## Significantly extended progression-free survival (PFS)—primary endpoint

**78% statistically significant reduction in the risk of death or progression (independent review)**




**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| IMBRUVICA® | 195 | 183 | 116 | 38 | 7 | 0 |
| Ofatumumab | 196 | 161 | 83 | 15 | 1 | 0 |

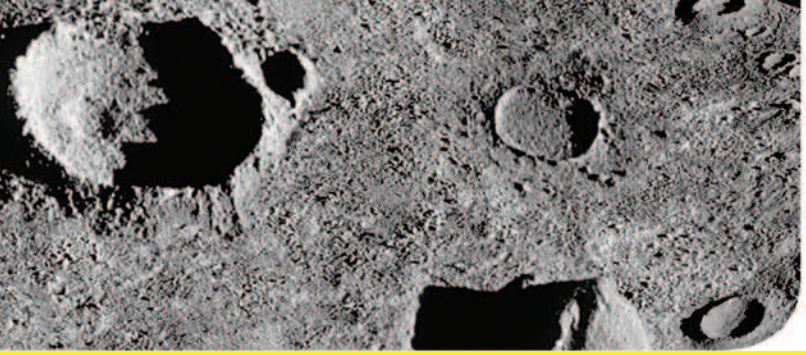
Results from the randomized, multicenter, open-label, Phase 3 RESONATE™ trial of IMBRUVICA® vs ofatumumab in patients with previously treated CLL. Patients (N=391) were randomized 1:1 to receive either IMBRUVICA® 420 mg orally daily until disease progression or unacceptable toxicity or IV ofatumumab at an initial dose of 300 mg, followed 1 week later by a dose of 2000 mg weekly for 7 doses, and then every 4 weeks for 4 additional doses. Fifty-seven patients randomized to ofatumumab crossed over following Independent Review Committee-confirmed progression to receive IMBRUVICA®. Primary endpoint: PFS as assessed by an Independent Review Committee (IRC) according to modified International Workshop on CLL Criteria.

## Significantly improved PFS in patients with previously treated del 17p CLL

- 75% reduced risk of progression or death (HR=0.25; 95% CI: 0.14, 0.45)
  - Median PFS not reached with IMBRUVICA® vs 5.8 months with ofatumumab

## In CLL studies, approximately 5% of patients discontinued due to adverse events

**Please review the Important Safety Information on adjacent page.**



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# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS

**Hemorrhage** - Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving anti-platelet or anti-coagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

**Infections** - Fatal and non-fatal infections have occurred with IMBRUVICA®. Twenty-six percent of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

**Cytopenias** - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

**Atrial Fibrillation** - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

**Second Primary Malignancies** - Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

**Embryo-Fetal Toxicity** - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

## ADVERSE REACTIONS

The most common adverse reactions (≥20%) in the clinical trials were thrombocytopenia (56%), neutropenia (51%), diarrhea (51%), anemia (37%), fatigue (28%), musculoskeletal pain (28%), upper respiratory tract infection (28%), rash (26%), nausea (25%), and pyrexia (24%). Approximately 5% of patients receiving IMBRUVICA® discontinued treatment due to adverse events. These included infections, subdural hematomas, and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

## DRUG INTERACTIONS

**CYP3A Inhibitors** - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

**CYP3A Inducers** - Avoid co-administration with strong CYP3A inducers.

## SPECIFIC POPULATIONS

**Hepatic Impairment** - Avoid use in patients with baseline hepatic impairment.

**Please review the Brief Summary of full Prescribing Information on the following page.**

To learn more, visit us at
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**Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)**

**IMBRUVICA® (ibrutinib) capsules, for oral use**

See package insert for Full Prescribing Information

## INDICATIONS AND USAGE

**Mantle Cell Lymphoma:** IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in full Prescribing Information].*

**Chronic Lymphocytic Leukemia:** IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in full Prescribing Information].*

**Chronic Lymphocytic Leukemia with 17p deletion:** IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion *[see Clinical Studies (14.2) in full Prescribing Information].*

## CONTRAINDICATIONS

None

## WARNINGS AND PRECAUTIONS

**Hemorrhage:** Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in full Prescribing Information].*

**Infections:** Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Twenty-five percent of patients with MCL and 26% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) *[See Adverse Reactions]*. Monitor patients for fever and infections and evaluate promptly.

**Cytopenias:** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

**Atrial Fibrillation:** Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3) in full Prescribing Information].*

**Second Primary Malignancies:** Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

**Embryo-Fetal Toxicity:** Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

## ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

**Mantle Cell Lymphoma:** The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.



The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

**Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Gastrointestinal disorders** | Diarrhea | 51 | 5 |
| | Nausea | 31 | 0 |
| | Constipation | 25 | 0 |
| | Abdominal pain | 24 | 5 |
| | Vomiting | 23 | 0 |
| | Stomatitis | 17 | 1 |
| | Dyspepsia | 11 | 0 |
| **Infections and infestations** | Upper respiratory tract infection | 34 | 0 |
| | Urinary tract infection | 14 | 3 |
| | Pneumonia | 14 | 7 |
| | Skin infections | 14 | 5 |
| | Sinusitis | 13 | 1 |
| **General disorders and administrative site conditions** | Fatigue | 41 | 5 |
| | Peripheral edema | 35 | 3 |
| | Pyrexia | 18 | 1 |
| | Asthenia | 14 | 3 |
| **Skin and subcutaneous tissue disorders** | Bruising | 30 | 0 |
| | Rash | 25 | 3 |
| | Petechiae | 11 | 0 |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain | 37 | 1 |
| | Muscle spasms | 14 | 0 |
| | Arthralgia | 11 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea | 27 | 4 |
| | Cough | 19 | 0 |
| | Epistaxis | 11 | 0 |
| **Metabolism and nutrition disorders** | Decreased appetite | 21 | 2 |
| | Dehydration | 12 | 4 |
| **Nervous system disorders** | Dizziness | 14 | 0 |
| | Headache | 13 | 0 |

**Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)**

| | Percent of Patients (N=111) | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 57 | 17 |
| Neutrophils Decreased | 47 | 29 |
| Hemoglobin Decreased | 41 | 9 |

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

**Chronic Lymphocytic Leukemia:** The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included

48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

***Study 1:*** Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

**Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Gastrointestinal disorders** | Diarrhea | 63 | 4 |
| | Constipation | 23 | 2 |
| | Nausea | 21 | 2 |
| | Stomatitis | 21 | 0 |
| | Vomiting | 19 | 2 |
| | Abdominal pain | 15 | 0 |
| | Dyspepsia | 13 | 0 |
| **Infections and infestations** | Upper respiratory tract infection | 48 | 2 |
| | Sinusitis | 21 | 6 |
| | Skin infection | 17 | 6 |
| | Pneumonia | 10 | 8 |
| | Urinary tract infection | 10 | 0 |
| **General disorders and administrative site conditions** | Fatigue | 31 | 4 |
| | Pyrexia | 25 | 2 |
| | Peripheral edema | 23 | 0 |
| | Asthenia | 13 | 4 |
| | Chills | 13 | 0 |
| **Skin and subcutaneous tissue disorders** | Bruising | 54 | 2 |
| | Rash | 27 | 0 |
| | Petechiae | 17 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Cough | 19 | 0 |
| | Oropharyngeal pain | 15 | 0 |
| | Dyspnea | 10 | 0 |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain | 27 | 6 |
| | Arthralgia | 23 | 0 |
| | Muscle spasms | 19 | 2 |
| **Nervous system disorders** | Dizziness | 21 | 0 |
| | Headache | 19 | 2 |
| | Peripheral neuropathy | 10 | 0 |
| **Metabolism and nutrition disorders** | Decreased appetite | 17 | 2 |
| **Neoplasms benign, malignant, unspecified** | Second malignancies* | 10* | 0 |
| **Injury, poisoning and procedural complications** | Laceration | 10 | 2 |
| **Psychiatric disorders** | Anxiety | 10 | 0 |
| | Insomnia | 10 | 0 |
| **Vascular disorders** | Hypertension | 17 | 8 |

**One patient death due to histiocytic sarcoma.*

**Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1**

| | Percent of Patients (N=48) | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 71 | 10 |
| Neutrophils Decreased | 54 | 27 |
| Hemoglobin Decreased | 44 | 0 |

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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***Study 2:*** Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

**Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2**

| System Organ Class ADR Term | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 48 | 4 | 18 | 2 |
| Nausea | 26 | 2 | 18 | 0 |
| Stomatitis* | 17 | 1 | 6 | 1 |
| Constipation | 15 | 0 | 9 | 0 |
| Vomiting | 14 | 0 | 6 | 1 |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 28 | 2 | 30 | 2 |
| Pyrexia | 24 | 2 | 15 | 1 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 16 | 1 | 11 | 2 |
| Pneumonia* | 15 | 10 | 13 | 9 |
| Sinusitis* | 11 | 1 | 6 | 0 |
| Urinary tract infection | 10 | 4 | 5 | 1 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash* | 24 | 3 | 13 | 0 |
| Petechiae | 14 | 0 | 1 | 0 |
| Bruising* | 12 | 0 | 1 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal Pain* | 28 | 2 | 18 | 1 |
| Arthralgia | 17 | 1 | 7 | 0 |
| **Nervous system disorders** | | | | |
| Headache | 14 | 1 | 6 | 0 |
| Dizziness | 11 | 0 | 5 | 0 |
| **Injury, poisoning and procedural complications** | | | | |
| Contusion | 11 | 0 | 3 | 0 |
| **Eye disorders** | | | | |
| Vision blurred | 10 | 0 | 3 | 0 |

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

**Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2**

| | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Neutrophils Decreased | 51 | 23 | 57 | 26 |
| Platelets Decreased | 52 | 5 | 45 | 10 |
| Hemoglobin Decreased | 36 | 0 | 21 | 0 |

* Based on laboratory measurements per IWCLL criteria

## DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

**CYP3A Inhibitors:** In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased $C_{max}$ and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in full Prescribing Information].*

**CYP3A Inducers:** Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib $C_{max}$ and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** Pregnancy Category D *[see Warnings and Precautions].*

*Risk Summary:* Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

*Animal Data:* Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

**Nursing Mothers:** It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

**Geriatric Use:** Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in full Prescribing Information].*

IMBRUVICA® (ibrutinib) capsules

**Renal Impairment:** Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

**Hepatic Impairment:** Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

**Females and Males of Reproductive Potential:** Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations].*

## PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills) suggestive of infection *[see Warnings and Precautions].*
- *Atrial Fibrillation:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.5) in full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics, Inc.
Sunnyvale, CA USA 94085
and
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PRC-00524 07/14

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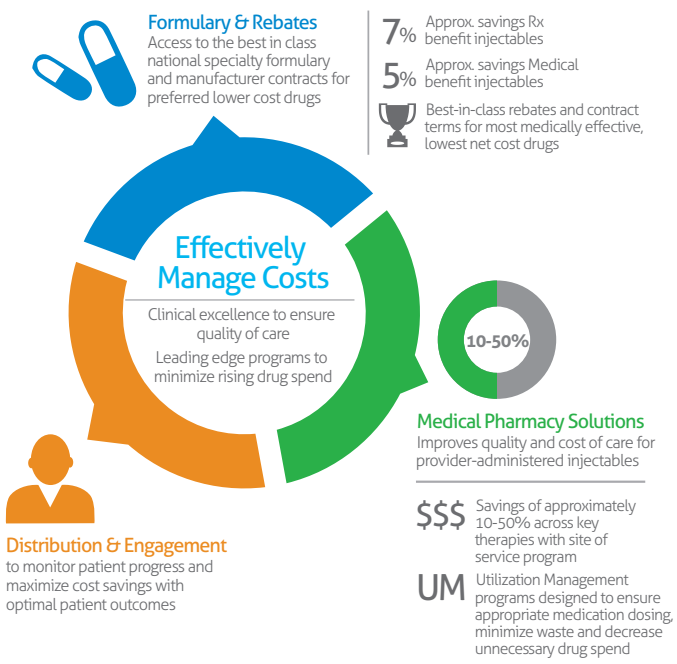


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Patients with type 1 diabetes

Levemir® is the FIRST and ONLY Pregnancy Category B basal insulin analog designated and FDA-approved for members with type 1 diabetes as young as 2 years old[1,a]

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Printed in the U.S.A. 0414-00020931-1 July 2014

## Indications and Usage

- Levemir® (insulin detemir [rDNA origin] injection) is indicated to improve glycemic control in adults and children with diabetes mellitus.

### Important Limitations of Use

- Levemir® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

## Important Safety Information

### Contraindications

- Levemir® is contraindicated in patients with hypersensitivity to Levemir® or any of its excipients.

### Warnings and Precautions

- **Dosage adjustment and monitoring:** Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.
- **Administration:** Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur. **Needles, insulin pens, or syringes should never be shared.**
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening. When a GLP-1 receptor agonist is used in combination with Levemir®, the Levemir® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia.
- **Hypersensitivity and allergic reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®.
- **Renal and hepatic impairment:** Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.
- **Drug interactions:** Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia.
- **Fluid retention and heart failure with concomitant use of PPAR-gamma agonists:** Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Levemir®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered.

### Adverse Reactions

- Adverse reactions associated with Levemir® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash, pruritus, and if taken with a GLP-1 receptor agonist, diarrhea.

### Use in Specific Populations

- Levemir® has not been studied in children with type 2 diabetes or in children with type 1 diabetes who are younger than 2 years of age.
- The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia.

**Please see accompanying brief summary of Prescribing Information on the following pages.**

## In pregnant women with type 1 diabetes:

- No differences in pregnancy outcomes or fetal and newborn health with Levemir® use compared to NPH insulin[1]
- Comparable A1C reductions vs NPH insulin[2,b]
- Significantly lower mean FPG with Levemir® vs NPH at gestational weeks 24 (96.8 mg/dL vs 113.8 mg/dL, *P*=0.012) and 36 (85.7 mg/dL vs 97.4 mg/dL, *P*=0.017)[2,b]
- Severe hypoglycemia rates comparable to NPH insulin (1.1 events per patient-year for the Levemir® group, 1.2 events per patient-year for the NPH insulin group)[1,c]

## In children and adolescents:

- FDA-approved in members with type 1 diabetes 2 years of age and older[1,a]
- Mean A1C values over 52 weeks were similar in both groups (Levemir®; 8.75%; NPH insulin; 8.64%)[3]
  – Rates of nonsevere hypoglycemia were comparable[1,a]
- Levemir®: 56.1 events/patient/year; NPH insulin: 70.7 events/patient/year

[a]Levemir® has not been studied in children with type 2 diabetes or in children with type 1 diabetes younger than 2 years of age.[1]

[b]An open-label, randomized, parallel-group, multinational study in women with type 1 diabetes who were on insulin for at least 12 months before randomization and who were planning to become pregnant or already pregnant at gestational weeks (GW) 8 to 12. Patients could enroll in the study with intention to become pregnant. Patients were withdrawn from the trial if they did not become pregnant within 1 year. Patients were separated at randomization as pregnant and nonpregnant and all were required to have A1C ≤8% at confirmation of pregnancy. Patients were randomized 1:1 to Levemir® (n=152) or NPH insulin (n=158). Both groups used a rapid-acting insulin as mealtime insulin. Approximately 50% of the women also received Levemir® or NPH insulin prior to conception and in the first 8 weeks of gestation. Regimen was followed from randomization until termination/6 weeks post delivery.[1,2]

[c]Nonsevere=PG <56 mg/dL (blood glucose [BG] <50 mg/dL) with or without symptoms (patient able to self-treat). Severe=event with symptoms consistent with hypoglycemia and associated with either a PG <56 mg/dL (BG <50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration (patient unable to self-treat).[1]

**References: 1.** Levemir® [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2013. **2.** Mathiesen ER, Hod M, Ivanisevic M, et al; Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care.* 2012;35(10):2012-2017. **3.** Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with type 1 diabetes: a 52-week randomized clinical trial. *Diabet Med.* 2013;30:216-225.


**Needles are sold separately and may require a prescription in some states.**

Levemir® FlexTouch®

*insulin detemir (rDNA origin) injection*

**LEVEMIR® (insulin detemir [rDNA origin] injection)**

**Rx ONLY**

**BRIEF SUMMARY: Please consult package insert for full prescribing information.**

**INDICATIONS AND USAGE:** LEVEMIR® is indicated to improve glycemic control in adults and children with diabetes mellitus. Important Limitations of Use: LEVEMIR® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

**CONTRAINDICATIONS:** LEVEMIR® is contraindicated in patients with hypersensitivity to LEVEMIR® or any of its excipients. Reactions have included anaphylaxis.

**WARNINGS AND PRECAUTIONS: Dosage adjustment and monitoring:** Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment. As with all insulin preparations, the time course of action for LEVEMIR® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity. **Administration:** LEVEMIR® should only be administered subcutaneously. Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycemia. Do not use LEVEMIR® in insulin infusion pumps. Do not dilute or mix LEVEMIR® with any other insulin or solution. If LEVEMIR® is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR® and the mixed insulin may be altered in an unpredictable manner. **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR®. The risk of hypoglycemia increases with intensive glycemic control. When a GLP-1 receptor agonist is used in combination with LEVEMIR®, the LEVEMIR® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia. All patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia. The prolonged effect of subcutaneous LEVEMIR® may delay recovery from hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. **Hypersensitivity and allergic reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR®. **Renal Impairment:** No difference was observed in the pharmacokinetics of insulin detemir between non-diabetic individuals with renal impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal impairment. **Hepatic Impairment:** Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment. **Drug interactions:** Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia. **Fluid retention and heart failure with concomitant use of PPAR-gamma agonists:** Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including LEVEMIR®, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

**ADVERSE REACTIONS:** The following adverse reactions are discussed elsewhere: Hypoglycemia; Hypersensitivity and allergic reactions. **Clinical trial experience:** Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1-4 below. See Tables 5 and 6 for the hypoglycemia findings. In the LEVEMIR® add-on to liraglutide+metformin trial, all patients received liraglutide 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 LEVEMIR® or continued, unchanged treatment with liraglutide 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with liraglutide 1.8 mg + metformin (11.7%) and greater than in patients treated with liraglutide 1.8 mg and metformin alone (6.9%). In two pooled trials, a total of 1155 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=767) or NPH (n=388). The mean duration of exposure to LEVEMIR® was 153 days, and the total exposure to LEVEMIR® was 321 patient-years. The most common adverse reactions are summarized in Table 1.

**Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)**

| | LEVEMIR®, % (n = 767) | NPH, % (n = 388) |
|---|---|---|
| Upper respiratory tract infection | 26.1 | 21.4 |
| Headache | 22.6 | 22.7 |
| Pharyngitis | 9.5 | 8.0 |
| Influenza-like illness | 7.8 | 7.0 |
| Abdominal Pain | 6.0 | 2.6 |

A total of 320 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=161) or insulin glargine (n=159). The mean duration of exposure to LEVEMIR® was 176 days, and the total exposure to LEVEMIR® was 78 patient-years. The most common adverse reactions are summarized in Table 2.

**Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR® to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)**

| | LEVEMIR®, % (n = 161) | Glargine, % (n = 159) |
|---|---|---|
| Upper respiratory tract infection | 26.7 | 32.1 |
| Headache | 14.3 | 19.5 |
| Back pain | 8.1 | 6.3 |
| Influenza-like illness | 6.2 | 8.2 |
| Gastroenteritis | 5.6 | 4.4 |
| Bronchitis | 5.0 | 1.9 |

In two pooled trials, a total of 869 adults with type 2 diabetes were exposed to individualized doses of LEVEMIR® (n=432) or NPH (n=437). The mean duration of exposure to LEVEMIR® was 157 days, and the total exposure to LEVEMIR® was 186 patient-years. The most common adverse reactions are summarized in Table 3.

**Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence ≥ 5%)**

| | LEVEMIR®, % (n = 432) | NPH, % (n = 437) |
|---|---|---|
| Upper respiratory tract infection | 12.5 | 11.2 |
| Headache | 6.5 | 5.3 |

A total of 347 children and adolescents (6-17 years) with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=232) or NPH (n=115). The mean duration of exposure to LEVEMIR® was 180 days, and the total exposure to LEVEMIR® was 114 patient-years. The most common adverse reactions are summarized in Table 4.

**Table 4: Adverse reactions (excluding hypoglycemia) in one 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)**

| | LEVEMIR®, % (n = 232) | NPH, % (n = 115) |
|---|---|---|
| Upper respiratory tract infection | 35.8 | 42.6 |
| Headache | 31.0 | 32.2 |
| Pharyngitis | 17.2 | 20.9 |
| Gastroenteritis | 16.8 | 11.3 |
| Influenza-like illness | 13.8 | 20.9 |
| Abdominal pain | 13.4 | 13.0 |
| Pyrexia | 10.3 | 6.1 |
| Cough | 8.2 | 4.3 |
| Viral infection | 7.3 | 7.8 |
| Nausea | 6.5 | 7.0 |
| Rhinitis | 6.5 | 3.5 |
| Vomiting | 6.5 | 10.4 |

**Pregnancy:** A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. *Hypoglycemia:* Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR®. Tables 5 and 6 summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR® clinical trials. For the adult trials and one of the pediatric trials (Study D), severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a plasma glucose value below 56 mg/dL (blood glucose below 50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. For the other pediatric trial (Study I), severe hypoglycemia was defined as an event with semi-consciousness, unconsciousness, coma and/or convulsions in a patient who could not assist in the treatment and who may have required glucagon or intravenous glucose. For the adult trials and pediatric Study D, non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (or equivalently blood glucose <50 mg/dL as used in Study A and C) that was self-treated by the patient. For pediatric Study I, non-severe hypoglycemia included asymptomatic events with plasma glucose <65 mg/dL as well as symptomatic events that the patient could self-treat or treat by taking oral therapy provided by the caregiver. The rates of hypoglycemia in the LEVEMIR® clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR®-treated patients and non-LEVEMIR®-treated patients (see Tables 5 and 6).

**Table 5: Hypoglycemia in Patients with Type 1 Diabetes**

| | | Severe Hypoglycemia | | Non-Severe Hypoglycemia | |
|---|---|---|---|---|---|
| | | Percent of patients with at least 1 event (n/total N) | Event/patient/year | Percent of patients (n/total N) | Event/patient/year |
| Study A, Type 1 Diabetes, Adults, 16 weeks In combination with insulin aspart | Twice-Daily LEVEMIR® | 8.7 (24/276) | 0.52 | 88.0 (243/276) | 26.4 |
| | Twice-Daily NPH | 10.6 (14/132) | 0.43 | 89.4 (118/132) | 37.5 |
| Study B, Type 1 Diabetes, Adults, 26 weeks In combination with insulin aspart | Twice-Daily LEVEMIR® | 5.0 (8/161) | 0.13 | 82.0 (132/161) | 20.2 |
| | Once-Daily Glargine | 10.1 (16/159) | 0.31 | 77.4 (123/159) | 21.8 |
| Study C, Type 1 Diabetes, Adults, 24 weeks In combination with regular insulin | Once-Daily LEVEMIR® | 7.5 (37/491) | 0.35 | 88.4 (434/491) | 31.1 |
| | Once-Daily NPH | 10.2 (26/256) | 0.32 | 87.9 (225/256) | 33.4 |
| Study D, Type 1 Diabetes, Pediatrics, 26 weeks In combination with insulin aspart | Once- or Twice Daily LEVEMIR® | 15.9 (37/232) | 0.91 | 93.1 (216/232) | 31.6 |
| | Once- or Twice Daily NPH | 20.0 (23/115) | 0.99 | 95.7 (110/115) | 37.0 |
| Study I, Type 1 Diabetes, Pediatrics, 52 weeks In combination with insulin aspart | Once- or Twice Daily LEVEMIR® | 1.7 (3/177) | 0.02 | 94.9 (168/177) | 56.1 |
| | Once- or Twice Daily NPH | 7.1 (12/170) | 0.09 | 97.6 (166/170) | 70.7 |

**Table 6: Hypoglycemia in Patients with Type 2 Diabetes**

| | | Study E, Type 2 Diabetes, Adults, 24 weeks In combination with oral agents | | Study F, Type 2 Diabetes, Adults, 22 weeks In combination with insulin aspart | | Study H, Type 2 Diabetes, Adults, 26 weeks in combination with Liraglutide and Metformin | |
|---|---|---|---|---|---|---|---|
| | | Twice-Daily LEVEMIR® | Twice-Daily NPH | Once- or Twice Daily LEVEMIR® | Once- or Twice Daily NPH | Once Daily LEVEMIR® + Liraglutide + Metformin | Liraglutide + Metformin |
| Severe hypoglycemia | Percent of patients with at least 1 event (n/total N) | 0.4 (1/237) | 2.5 (6/238) | 1.5 (3/195) | 4.0 (8/199) | 0 | 0 |
| | Event/patient/year | 0.01 | 0.08 | 0.04 | 0.13 | 0 | 0 |
| Non-severe hypoglycemia | Percent of patients (n/total N) | 40.5 (96/237) | 64.3 (153/238) | 32.3 (63/195) | 32.2 (64/199) | 9.2 (15/163) | 1.3 (2/158*) |
| | Event/patient/year | 3.5 | 6.9 | 1.6 | 2.0 | 0.29 | 0.03 |

*One subject 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

*Insulin Initiation and Intensification of Glucose Control:* Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. *Lipodystrophy:* Long-term use of insulin, including LEVEMIR®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy. *Weight Gain:* Weight gain can occur with insulin therapy, including LEVEMIR®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. *Peripheral Edema:* Insulin, including LEVEMIR®, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. *Allergic Reactions: Local Allergy:* As with any insulin therapy, patients taking LEVEMIR® may experience injection site reactions, including localized erythema, pain, pruritus, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR® reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy. Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks. *Systemic Allergy:* Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR®, and may be life-threatening. *Antibody Production:* All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LEVEMIR®, antibody development has been observed with no apparent impact on glycemic control. **Postmarketing experience:** The following adverse reactions have been identified during post approval use of LEVEMIR®. 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. Medication errors have been reported during post-approval use of LEVEMIR® in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR®. To avoid medication errors between LEVEMIR® and other insulins, patients should be instructed always to verify the insulin label before each injection.

**OVERDOSAGE:** An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

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

For information about LEVEMIR® contact:
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www.novonordisk-us.com

Manufactured by:
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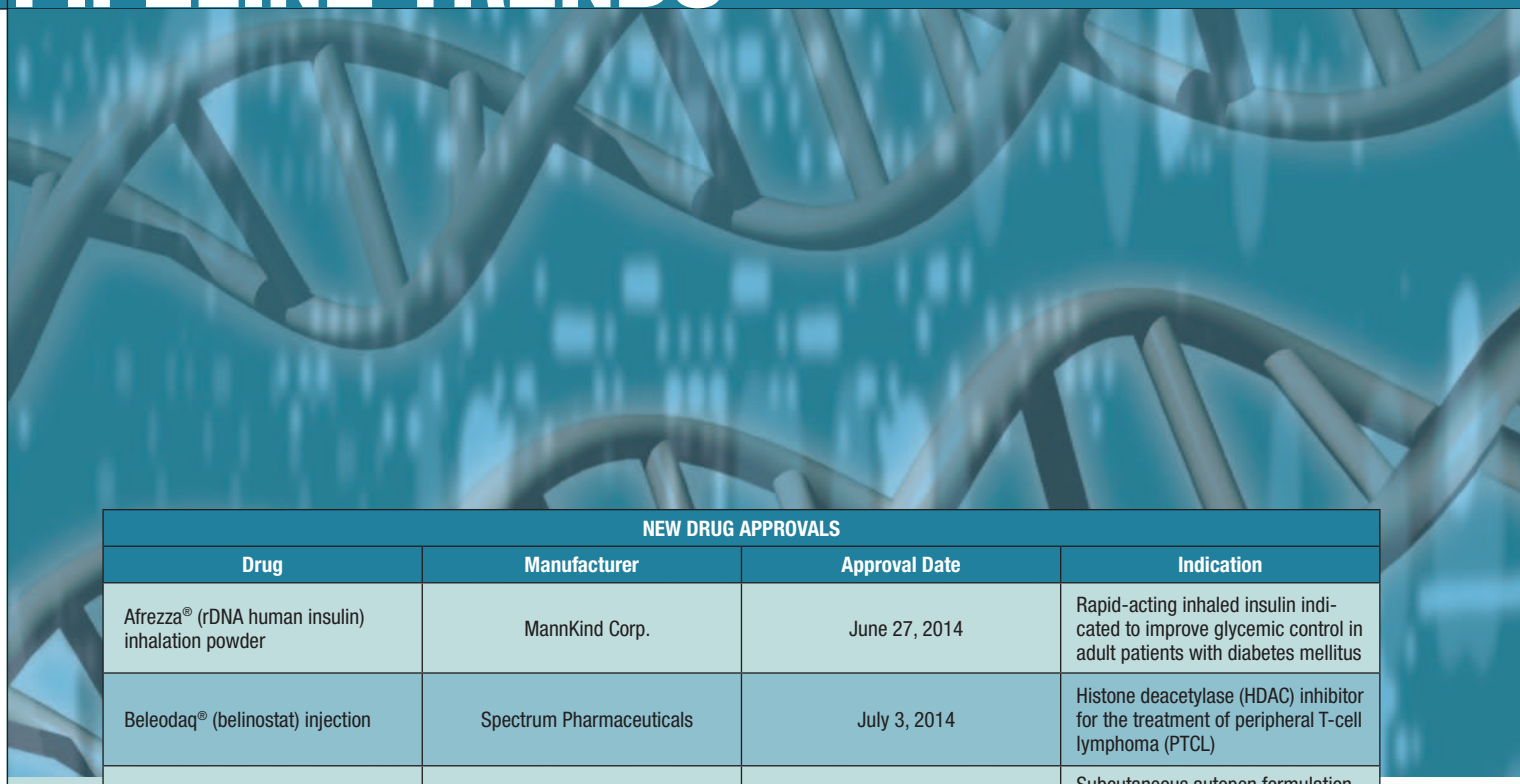
0314-00020331-1 3/2014

novo nordisk®

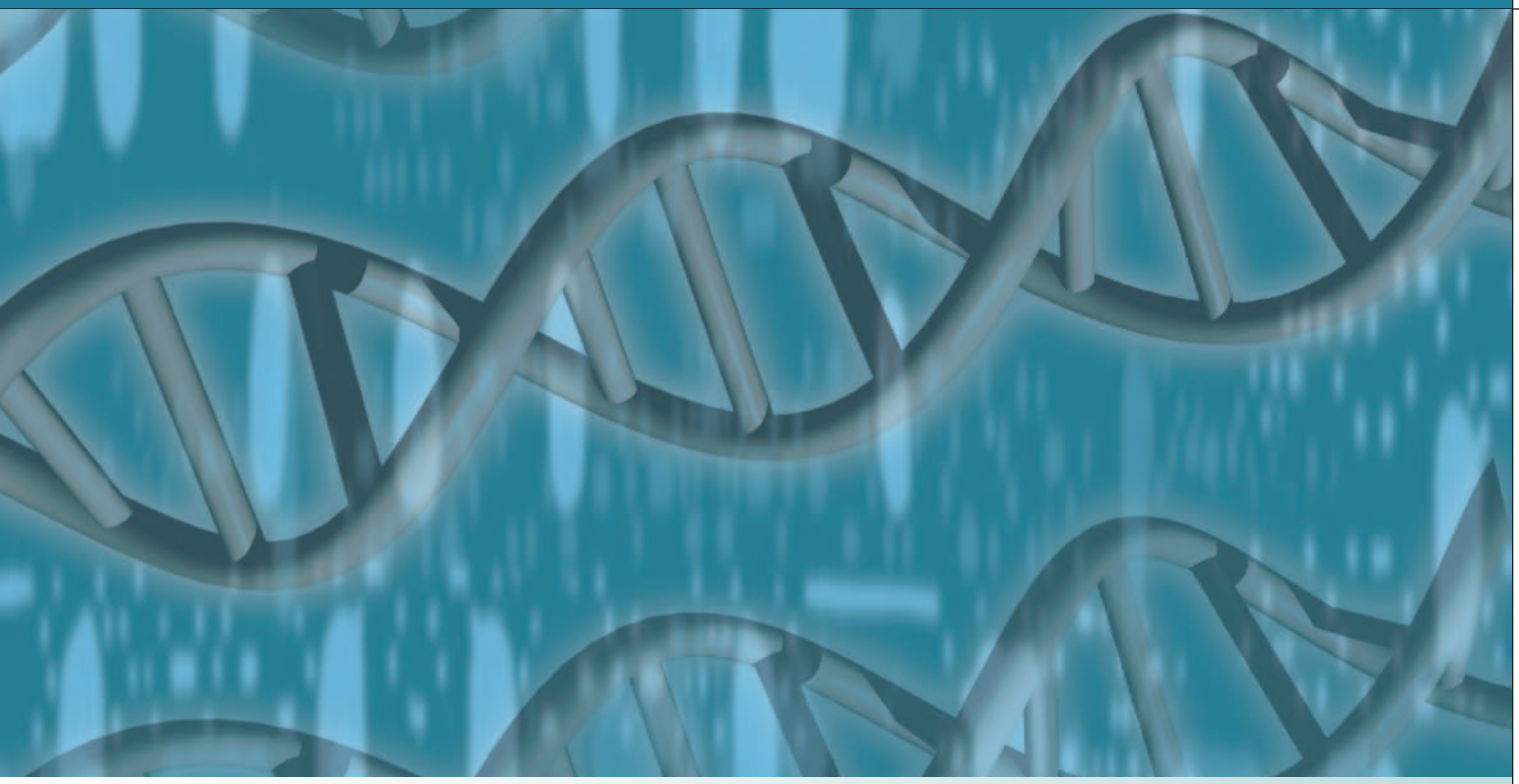
Levemir®
*insulin detemir (rDNA origin) injection*

# PIPELINE TRENDS



| NEW DRUG APPROVALS | | | |
|---|---|---|---|
| **Drug** | **Manufacturer** | **Approval Date** | **Indication** |
| Afrezza® (rDNA human insulin) inhalation powder | MannKind Corp. | June 27, 2014 | Rapid-acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus |
| Beleodaq® (belinostat) injection | Spectrum Pharmaceuticals | July 3, 2014 | Histone deacetylase (HDAC) inhibitor for the treatment of peripheral T-cell lymphoma (PTCL) |
| Rasuvo™ (methotrexate) injection | Medac Pharma | July 11, 2014 | Subcutaneous autopen formulation of methotrexate for the treatment of severely active RA, polyarticular juvenile RA, and psoriasis |
| Ruconest® (recombinant C1 esterase inhibitor) injection | Salix | July 16, 2014 | C1 esterase inhibitor indicated for treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE) |
| Targiniq™ ER (naloxone/oxycodone) extended-release tablet | Purdue Pharma | July 23, 2014 | Opioid antagonist and opioid analgesic combination in a long-acting abuse-deterrent formulation for the management of chronic severe pain |
| Zydelig® (idelalisib) tablet | Gilead | July 23, 2014 | PI3K delta inhibitor for treatment of CLL, relapsed follicular B-cell non-Hodgkin's lymphoma, and relapsed small lymphocytic lymphoma |
| Striverdi® Respimat (olodaterol) inhalation | Boehringer Ingelheim | July 31, 2014 | Once-daily long-acting beta-agonist (LABA) for the maintenance treatment of chronic obstructive pulmonary disease (COPD) |
| Jardiance® (empagliflozin) tablet | Boehringer Ingelheim | August 1, 2014 | Sodium glucose co-transporter-2 (SGLT2) inhibitor for the treatment of type 2 diabetes |
| Invokamet™ (canagliflozin/metformin) tablet | Janssen | August 8, 2014 | Sodium glucose co-transporter-2 (SGLT2) inhibitor and biguanide combination for the treatment of type 2 diabetes |
| Belsomra® (suvorexant) tablet | Merck | August 12, 2014 | Orexin receptor antagonist for the treatment of insomnia |
| Plegridy™ (peginterferon beta-1a) injection | Biogen Idec | August 15, 2014 | Interferon beta for the treatment of patients with relapsing forms of multiple sclerosis |
| Cerdelga™ (eliglustat) capsule | Genzyme | August 19, 2014 | Glucosylceramide synthase inhibitor for the long-term treatment of adults with Gaucher disease type 1 |

**Disclosures:** The information contained in Pipeline Trends is current as of August 2014. Estimated dates are subject to change according to additional indication/approvals, patents, patent litigation, etc. Information available from **www.fda.gov** and **pricerx.medispan.com**.



### The Next Pharmaceutical Blockbusters: PCSK9 Inhibitors

In 2015, a new class of hyperlipidemia medications is expected to become commercially available. PCSK9 inhibitors are injectable biologic agents that have demonstrated profound success in reducing LDL cholesterol levels in patients with hypercholesterolemia that is not adequately controlled. With nearly 24 million Americans with uncontrolled LDL levels, the potential patient population for PCSK9 inhibitors is quite extensive. This generates legitimate economic concerns for managed care organizations. Although pricing is not yet available for the PCSK9 inhibitors, as these products are biologic agents, they are not anticipated to be inexpensive. In fact, the first two PCSK9 inhibitors expected to receive FDA approval are both projected to exceed $1 billion in sales each year, with some industry analysts projecting this to be a $10 billion drug class in the near future.

Although the outcomes associated with PCSK9 inhibitors appear to be superior to the current industry standards, managed care organizations should begin preparing themselves for the potential economic impact that may be associated with these agents. In addition, once PCSK9 inhibitors receive FDA approval, it will be important for health plans to develop appropriate use criteria that allows for the identification of high-risk patients to ensure optimization of cardiovascular outcomes, but also minimizes the potential cost burden that is likely to be associated with these products.

**NEW FDA-APPROVED INDICATIONS**

| Drug | Approval Date | Indication |
|---|---|---|
| Imbruvica® (ibrutinib) | July 28, 2014 | Expanded approval to treat patients with CLL with a 17p deletion |
| Eylea® (eflibercept) | July 29, 2014 | Expanded approval for the treatment of diabetic macular edema (DME) |
| Avastin® (bevacizumab) | August 14, 2014 | Expanded indication to treat patients with persistent, recurrent, or late-stage (metastatic) cervical cancer |

**NEW FORMULATIONS AND DOSAGE FORMS**

| Drug | Approval Date | Advertised Advantage |
|---|---|---|
| Flonase® (fluticasone propionate) nasal spray | July 23, 2014 | Now available over the counter (OTC) |

**NEW FIRST-TIME GENERIC DRUG APPROVALS**

Valsartan (Diovan®) tablet: Approved June 26, 2014

**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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