

Magellan Rx Report

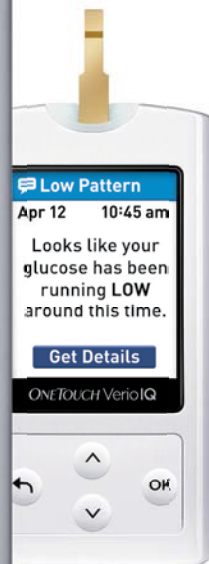
MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Specialty Management Solutions:

Multiple Sclerosis
Rheumatoid Arthritis
Hepatitis C

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MANAGEMENTSM

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**WHAT DID YOUR
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Meet OneTouch® Verio® IQ.

The first meter ever with PatternAlert™ Technology.

Every time you test, it looks for hidden patterns of high and low blood sugar, and alerts you when it finds one—right on screen.* The idea? You get more information for less work, right in the palm of your hand.†

Put it to the test. TryOneTouch.com.



*The meter uses results tagged "before meal" to find high patterns. Tagging is not necessary to find low patterns.

†When compared with using a paper logbook alone.

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Life First.
ONETOUCH®

Do any of these overactive bladder symptoms sound familiar?



Once I get the sudden urge to go to the bathroom, I can't wait.

YES ☐ NO ☐

I worry I might accidentally leak and sometimes wear pads.

YES ☐ NO ☐



Sometimes my bladder symptoms get in the way of things I like to do.

YES ☐ NO ☐

I've had enough, and I'm ready to do something about my urges and leaks.

YES ☐ NO ☐



If you answered "YES" to any of these, talk to your doctor about your symptoms and whether or not VESicare may be right for you.

Only your doctor can determine if you have overactive bladder. Once-daily VESicare is proven to treat overactive bladder with symptoms of frequent urges and leaks.* That's because it can help control your bladder muscle, day and night. So ask your doctor about taking care with VESicare.

*Results may vary.

USE AND DOSE

VESicare is for overactive bladder with symptoms of urgency, frequency, and leakage. The recommended dose of VESicare is 5 mg once daily. If the 5-mg dose is well tolerated, your doctor may increase the dose to 10 mg once daily.

IMPORTANT SAFETY INFORMATION

VESicare is not for everyone. If you have certain stomach or glaucoma problems, or trouble emptying your bladder, do not take VESicare. VESicare may cause allergic reactions that may be serious. If you experience swelling of the face, lips, throat or tongue, stop taking VESicare and get emergency help. Tell your doctor right away if you have severe abdominal pain, or become constipated for three or more days. VESicare may cause blurred vision, so use caution while driving or doing unsafe tasks. Common side effects are dry mouth, constipation, and indigestion.

Please see Important Patient Information on the following page.

FIRST 30-DAY PRESCRIPTION FREE[†]
at vesicare.com, or call (800) 403-6565.

[†]Subject to eligibility. Restrictions may apply.

To learn about financial assistance programs for VESicare, please call Astellas Reimbursement Services at 1-800-477-6472 or go to www.astellasreimbursement.com
011K-051-4637-1



Take care with
VESicare[®]
(solifenacin succinate)
tablets

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



Brief Summary based on FDA Approved Patient Labeling

VESicare® (VES-ih-care) (solifenacin succinate) tablets

Read the Patient Information that comes with VESicare before you start taking it and each time you get a refill. There may be new information. This summary does not take the place of talking with your doctor about your medical condition or treatment.

What is VESicare?

VESicare is a prescription medicine for **adults** used as treatment for symptoms of a condition called **overactive bladder**:

- Urgency: a strong need to urinate right away
- Leakage: leaking or wetting accidents—also called “urinary incontinence”
- Frequency: urinating often

It is not known if VESicare is safe and effective in children.

What is overactive bladder?

Overactive bladder occurs when you cannot control your bladder contractions. When these muscle contractions happen too often, or cannot be controlled, you can get symptoms of overactive bladder, which are urinary frequency, urinary urgency, and urinary incontinence (leakage).

Who should NOT take VESicare?

Do not take VESicare if you:

- are unable to empty your bladder (urinary retention)
- have delayed or slow emptying of your stomach (gastric retention)
- have an eye problem called “uncontrolled narrow-angle glaucoma”
- are allergic to solifenacin succinate or any of the ingredients in VESicare.

What should I tell my doctor?

Before taking VESicare, tell your doctor if you:

- have any stomach or intestinal problems or problems with constipation
- have trouble emptying your bladder or you have a weak urine stream
- have an eye problem called “narrow-angle glaucoma”
- have kidney or liver problems
- have a rare heart problem called “QT prolongation”
- are pregnant or plan to become pregnant. It is not known if VESicare will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VESicare passes into your breast milk. You and your doctor should decide if you will take VESicare OR breastfeed.

Tell your doctor about all the medicines and supplements you take.

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. VESicare may affect the way other medicines work, and other medicines may affect how VESicare works.

How should I take VESicare?

Take VESicare exactly as your doctor tells you to take it.

- Take 1 VESicare tablet 1 time a day.
- Take VESicare with water and **swallow the tablet whole**.
- You can take VESicare with or without food.
- If you miss a dose of VESicare, begin taking VESicare again the next day. Do not take 2 doses of VESicare the same day.
- If you take too much VESicare, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking VESicare?

VESicare can cause blurred vision or drowsiness. Do not drive or operate heavy machinery until you know how VESicare affects you.

What are the possible side effects of VESicare?

VESicare may cause serious side effects including:

- **Serious allergic reaction.** Stop taking VESicare and get medical help right away if you have:
 - hives, skin rash or swelling
 - severe itching
 - swelling of your face, mouth or tongue
 - trouble breathing

The **most common side effects** of VESicare include:

- dry mouth
- constipation. Call your doctor if you get severe stomach area (abdominal) pain or become constipated for 3 or more days.
- urinary tract infection
- blurred vision
- heat exhaustion or heat stroke. This can happen when VESicare is used in hot environments. Symptoms may include:
 - decreased sweating
 - dizziness
 - tiredness
 - nausea
 - increase in body temperature

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

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

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

How should I store VESicare?

- Keep the bottle closed.
- Store VESicare at 59°F to 86°F (15°C to 30°C).
- Safely throw away medicine that is out of date or that you no longer need.

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

General information about VESicare.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information. Do not use VESicare for a condition for which it was not prescribed. Do not give VESicare to other people, even if they have the same symptoms you have. It may harm them.

This is a summary of the most important information about VESicare. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about VESicare that is written for health professionals.

For more information, visit www.vesicare.com or call (800) 727-7003.

Rx Only

Manufactured by:

Astellas Pharma Technologies, Inc.
Norman, Oklahoma 73072

Marketed and Distributed by:

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Deerfield, Illinois 60015-2548

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011K-051-4680

VIOKACE™ (pancrelipase) tablets, for oral use

Brief Summary of Prescribing Information for VIOKACE (pancrelipase). See package insert for full prescribing information.

INDICATIONS AND USAGE

VIOKACE (pancrelipase) is a combination of porcine-derived lipases, proteases, and amylases. VIOKACE, in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Fibrosing Colonopathy: Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day [see *Dosage and Administration* (2.2) in full prescribing information]. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

Potential for Irritation to Oral Mucosa: Care should be taken to ensure that no drug is retained in the mouth to avoid irritation of oral mucosa, and/or loss of enzyme activity. VIOKACE should not be crushed or chewed [see *Dosage and Administration* (2.1) and *Patient Counseling Information* (17.1) in full prescribing information].

Potential for Risk of Hyperuricemia: Caution should be exercised when prescribing VIOKACE to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

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

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

Potential for Exacerbation of Symptoms of Lactose Intolerance: VIOKACE tablets contain lactose monohydrate. Patients who have lactose intolerance may not be able to tolerate VIOKACE.

ADVERSE REACTIONS

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) that are described elsewhere in the label include fibrosing colonopathy, hyperuricemia and allergic reactions [see *Warnings and Precautions*].

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The short-term safety of VIOKACE was assessed in a single, multicenter, randomized, parallel, placebo-controlled, double-blind study of 50 patients, ages 24-70 years, with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or pancreatectomy. VIOKACE Tablets (20,880 USP units of lipase per tablet) or placebo were administered as 22 tablets per day (6 tablets with 3 meals and 2 tablets with 2 of 3 snacks). Duration of exposure ranged from 6 to 7 days. The majority of the subjects were Caucasian (96%) and male (82%).

The most common adverse reactions (greater than or equal to 7%) were biliary tract stones and anal pruritus. Table 1 enumerates adverse reactions that occurred in at least 1 patient (greater than or equal to 3%) treated with VIOKACE at a higher rate than with placebo. Two adverse reactions reported in greater than one patient were biliary tract stones and anal pruritus.

TABLE 1 Adverse Reactions Occurring in at Least 1 Patient (greater than or equal to 3%) in Chronic Pancreatitis or Pancreatectomy		
MedDRA Primary System Organ Class/ Adverse Reactions	Treatment Group	
	VIOKACE (N=30)	Placebo (N=20)
Blood And Lymphatic System Disorders		
Anemia	1 (3%)	0
Gastrointestinal Disorders		
Anal pruritus	2 (7%)	0
Abdominal pain	1 (3%)	0
Ascites	1 (3%)	0
Flatulence	1 (3%)	0

TABLE 1 Adverse Reactions Occurring in at Least 1 Patient (greater than or equal to 3%) in Chronic Pancreatitis or Pancreatectomy (continued)

General Disorders and Administration Site Conditions		
Edema peripheral	1 (3%)	0
Hepatobiliary Disorders		
Biliary tract stones	2 (7%)	0
Hydrocholecystitis	1 (3%)	0
Infections and Infestations		
Viral infection	1 (3%)	0
Nervous System Disorders		
Headache	1 (3%)	0
Renal and Urinary Disorders		
Renal cyst	1 (3%)	0
Skin and Subcutaneous Tissue Disorders		
Rash	1 (3%)	0

Postmarketing Experience: Post-marketing data for VIOKACE have been available since 2003. The safety data are similar to that described below. 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.

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

Pediatric Use: The safety and effectiveness of VIOKACE in pediatric patients have not been established. In general, delayed-release (enteric-coated) capsules should be used for pediatric patients. Due to greater degradation in the gastric environment, VIOKACE, a non-enteric-coated, pancreatic enzyme replacement product, may have decreased bioavailability and therefore may be less efficacious than enteric-coated formulations. Thus, use of VIOKACE in pediatric patients may increase the risk of inadequate treatment of pancreatic insufficiency and result in suboptimal weight gain, malnutrition and/or need for larger doses of pancreatic enzyme replacement [see *Warnings and Precautions*]. The efficacy of VIOKACE was established in adult patients with concomitant proton pump inhibitor (PPI) therapy. The long-term safety of PPI use in pediatric patients has not been established.

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

OVERDOSAGE

There have been no reports of overdose in clinical trials or post-marketing surveillance with VIOKACE. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures [see *Dosage and Administration* (2) in full prescribing information and *Warnings and Precautions*]. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment [see *Warnings and Precautions*].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase.

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Birmingham, AL 35242 USA

Manufactured by:

Confab Laboratories, Inc.
St. Hubert, Canada

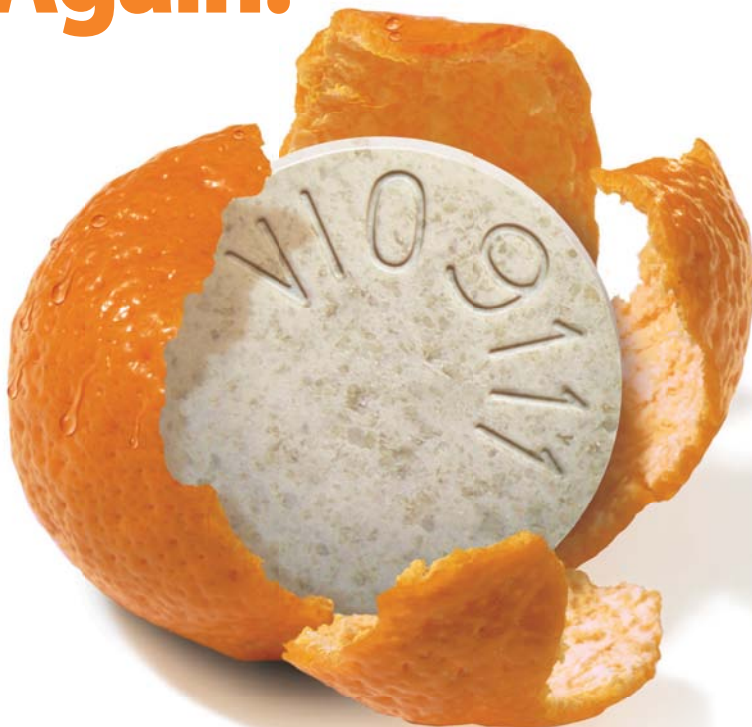
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In combination with a proton pump inhibitor (PPI), for the treatment of adults with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or pancreatectomy

When an uncoated pancreatic enzyme is your choice for your patients, VIOKACE™ is now available.

Uncover it. Again.



For more information about VIOKACE, please visit www.VIOKACE.com

Important Safety Information

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of VIOKACE exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)
- To avoid irritation of oral mucosa, do not chew VIOKACE or retain in the mouth
- Exercise caution when prescribing VIOKACE to patients with gout, renal impairment, or hyperuricemia
- There is theoretical risk of viral transmission with all pancreatic enzyme products including VIOKACE
- In rare cases, patients taking pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase) have experienced severe allergic reactions including anaphylaxis, asthma, hives, and pruritus. Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin
- VIOKACE tablets contain lactose monohydrate. Patients who have lactose intolerance may not be able to tolerate VIOKACE
- Adverse reactions occurring in at least 2 chronic pancreatitis or pancreatectomy patients (greater than or equal to 7%) receiving VIOKACE are biliary tract stones and anal pruritus
- The safety and effectiveness of VIOKACE in pediatric patients have not been established. VIOKACE use in pediatric patients may result in suboptimal growth due to tablet degradation in the gastric environment. In general, delayed release (enteric-coated) capsules should be used for pediatric patients
- VIOKACE is not interchangeable with any other pancrelipase product

Please read brief summary of US Prescribing Information for VIOKACE on the following page.



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Viokace™
(pancrelipase)
Tablets

WELCOME

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Letter from the President

Susan Petrovas

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Dear Managed Care Colleagues,

As many of you are aware, specialty pharmaceuticals are currently responsible for more than 20 to 25 percent of health plan drug costs. As this number is expected to increase to 40 to 50 percent in just a few years, an unsustainable financial burden will be placed upon the managed care industry. Now, more than ever, payors need to develop and implement cost-effective and clinically viable strategies to help contain this raising expenditure. The coordination of solutions for both the medical and pharmacy benefit will be integral to the successful management of specialty pharmaceuticals.

To date, CDMI has focused our clinical programs on improving outcomes within the traditional non-specialty pharmacy benefit for more than 25 payors, representing approximately 30 million patient lives. However, due to the reasons outlined above, our customers have asked us to explore strategic solutions to combat the growing specialty expenditure. In response to this request, CDMI will be analyzing industry trends and allocating a substantial amount of resources to the development of clinically sound and cost-effective management programs that will address this issue from both the medical and pharmacy benefit.

Among the strategies that CDMI is pursuing to appropriately manage specialty conditions is the development of clinical pathways of care (CPCs). These pathways are being developed and validated by specialized clinical practitioners and key industry thought leaders. Each pathway will be designed to improve the use of evidence-based guidelines, improve care coordination, and improve the use of preferred specialty products. In addition to providing consistent, evidenced-based care, the CDMI pathways are being designed to create the greatest potential for economic savings, while improving access to care coordination and maximizing outcomes.

CDMI is excited to implement these clinical initiatives along with the development of compliance/adherence programs within the specialty space. Star Rating improvements, where appropriate, and other patient-focused initiatives will be developed for our payor clients, as well. Our highly trained clinical staff is passionate about improving the health outcomes of patients suffering from chronic and debilitating conditions, and works in partnership with network physicians to ensure the greatest degree of healthcare quality is delivered.

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

Sincerely,

Susan C. Petrovas, RPh
President, CDMI



Susan Petrovas,
RPh, President

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

CALL FOR SUBMISSIONS



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

CDMI Report invites article submissions pertaining to the following subjects:

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

Disease States of Special Interest:

- Alzheimer's/Aging
- Asthma/COPD
- Cardiovascular Disease
- Diabetes
- Gastrointestinal Conditions
- Growth Hormone Deficiency
- Hepatitis C
- Immune Globulin Therapy
- Infertility
- Obesity
- Oncology
- Osteoarthritis
- Osteoporosis
- Overactive Bladder
- Mental Health
- Multiple Sclerosis
- Pain Management
- Rheumatoid Arthritis



MEDICAL AND PHARMACY BENEFIT MANAGEMENT

To learn more about CDMI and to view this publication online, visit us at www.CDMIhealth.com.

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

Rethinking Bone Marrow Transplants for Children with Leukemia

Failure of intensive chemotherapy induction is uncommon in children with acute lymphoblastic leukemia (ALL). But children who experience induction failure are at high risk for adverse outcomes and were traditionally considered candidates for bone marrow transplants.

An international group of researchers looked at survival rates in children who failed to achieve clinical remission during four to six weeks of induction chemotherapy. They found that the 10-year survival rate was 72 percent in children who had additional chemotherapy instead of bone marrow transplantation when induction failed. These patients had the type of ALL that affects B cells. About 85 percent of children with ALL have this form of the disease.

The researchers say their results demonstrate that consideration of a bone marrow transplant should not be automatic when children fail to achieve remission following induction chemotherapy. Bone marrow transplantation is a costly procedure that places patients at risk for immediate and chronic health issues. Additional chemotherapy may be easier on patients and more cost effective.

Source: Schrappe M. et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. *NEJM*. 2012;366(15):1371-1381.

Biologics May Help Rheumatoid Arthritis Patients Live Longer

Rheumatoid arthritis (RA) patients treated with biologic disease-modifying antirheumatic drugs (DMARDs) may have significantly lower mortality rates than patients treated with traditional oral DMARDs. German researchers conducted a study involving nearly 9,000 patients. Those who received oral DMARDs had a mortality rate of 20.6 percent. Patients who received biologic DMARDs had mortality rates from 10.6 to 12.7 percent, depending on the biologic DMARD they were using.

The researchers found that life expectancy was 2.2 years shorter for patients with RA, compared to the general population. They also evaluated participants using the Disease Activity Score Calculator (DAS28) and noted a strong association between disease activity and mortality risk. Participants with mean DAS28 scores below 4.1 had normal life expectancies. Those with mean scores above 4.1 saw decreases in life expectancy. Women in this category died 5.6 years before women of the same age in the general population. Men with mean scores above 4.1 died 4.8 years earlier than men who did not have RA.

This study demonstrates that treatment with biologic DMARDs may be an effective way to manage RA and extend patients' lives.

Source: Listing J. et al. Control of disease activity and treatment with biologics increases life expectancy in rheumatoid arthritis patients. Annual Congress of the European League Against Rheumatism. Berlin, Germany. 7 June 2012. Conference Presentation.

Hepatitis C Causing Liver Damage in Greater Numbers

Advanced liver disease caused by chronic hepatitis C virus (HCV) will become even more of a public health issue over the next few years. This is the prediction of researchers that assessed the future healthcare needs of patients with HCV.

The researchers found that more than 200,000 patients with HCV had advanced liver disease in 2008 and projected that an additional 300,000 patients with HCV would develop potentially life-threatening liver problems by 2015. The risk is significantly higher for baby boomers, who account for more than 80 percent of all cases of HCV. The researchers note that this rise in liver disease will place added stress on the U.S. healthcare system.

According to the researchers, this study illustrates the need for screening patients and diagnosing HCV early. Treatments for HCV are most effective before advanced liver disease develops.

Source: Kwong A. et al. Current and future disease progression of HCV-infected patients among different age cohorts. Digestive Disease Week Conference Presentation. May 2012. San Diego Convention Center, San Diego, CA.

Combination Therapy Improves Outlook for Patients with Pulmonary Arterial Hypertension

Patients with pulmonary arterial hypertension (PAH)

see more significant improvements with combined therapy when compared with monotherapy. Researchers recently reported the results of a meta-analysis of seven trials that evaluated 768 participants who received either combination or monotherapy.

There is no cure for PAH. Since no single medication produces consistent and continued results, combination therapy that targets multiple pathways is sometimes used.

This new study found that patients treated with combination therapy rather than a single agent saw improvements in exercise capacity as measured by the six-minute walk distance. In addition, they experienced a reduced risk of their condition worsening.

The study suggests that combination therapy is a viable option to help improve PAH patients' quality of life and reduce complications.

Source: Zhu B. et al. Combination therapy improves exercise capacity and reduces risk of clinical worsening in patients with pulmonary arterial hypertension: A meta-analysis. *J Cardiovasc Pharm.* 2012; epub ahead of print.

New Guidelines Urge Early and Aggressive Treatment for RA

Providers are encouraged to treat patients with early symptoms of rheumatoid arthritis (RA) aggressively. This is one of the major changes outlined in the new treatment guidelines recently released by the American College of Rheumatology. The new recommendations offer the first guidance for physicians since 2008 about how and when to use disease-modifying antirheumatic drugs (DMARDs) and biologics—the two main classes of RA medications.

The call for early and vigorous treatment may stem from growing opinions that RA causes irreversible damage. Intensive therapy may help preserve function, the ability to work, and quality of life.

The new recommendations vary for each patient. Generally, however, they recommend a DMARD as the first line of treatment. If more control is needed, the report suggests combining two or more oral DMARDs before progressing to the use of biologics. In addition, the guidelines encourage providers to make vaccinations and screenings a priority to help protect RA patients from tuberculosis, shingles, and other infections.

The new guidelines can help physicians provide the most up-to-date and effective treatment for their patients. Gaining control over the progression of RA can help improve quality of life and avoid costly complications.

Source: Singh J.A. et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care & Research.* 2012;64(5):625-639.

Survey Suggests MS Misdiagnosis is Common

Diagnosing multiple sclerosis (MS) can be difficult, despite initiatives designed to standardize criteria and help providers differentiate between conditions that may have similar symptoms. Researchers conducted an online survey of neurologists to determine how often they see patients who are misdiagnosed with MS—a situation that can have significant treatment, economic, and psychological implications for patients and families.

Ninety-five percent of physicians surveyed had seen at least one patient they felt had been misdiagnosed with MS the previous year. About 40 percent saw three to five patients who they believed were misdiagnosed during the same period. Many of these patients were taking disease-modifying MS therapies. Some of the conditions misdiagnosed as MS included nonspecific brain abnormalities, psychiatric diseases, migraines, and fibromyalgia.

There is no definitive diagnostic test for MS. An accompanying editorial noted that the misdiagnosis may be related to the over-reliance on magnetic resonance imaging (MRI). The author stated that providers should be confident of the diagnosis before prescribing long-term therapies that can be risky, uncomfortable, expensive, and inconvenient for patients.

Source: Solomon A. et al. "Undiagnosing" multiple sclerosis: The challenge of misdiagnosis in MS. *Neurology.* 2012; epub ahead of print.

Throughout the course of castration-resistant prostate cancer (CRPC)

THE ROOT OF TUMOR GROWTH

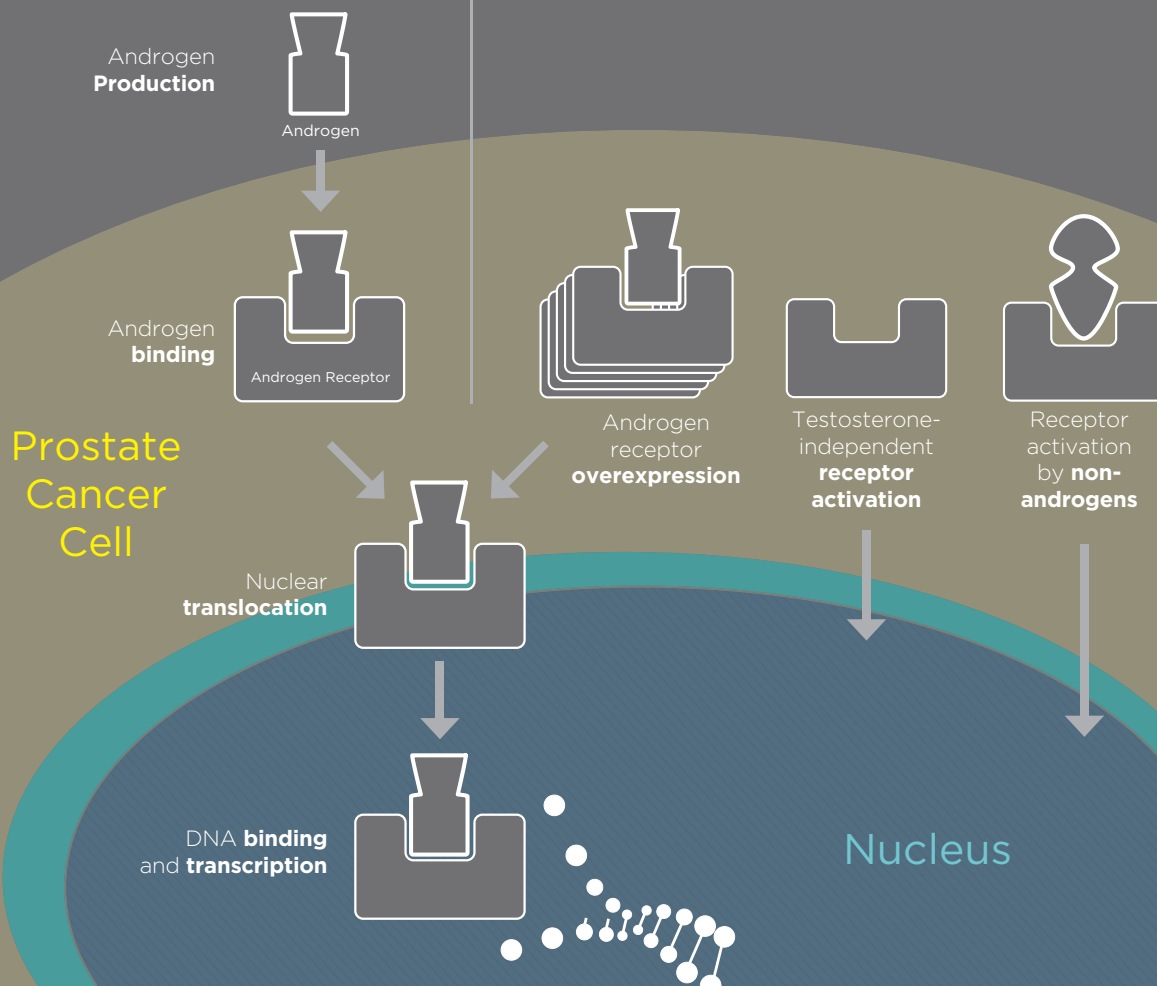
ANDROGEN RECEPTOR SIGNALING



- ▶ Androgen receptor signaling promotes tumor growth and drives prostate cancer progression.¹⁻³
- ▶ Despite low or undetectable levels of testosterone, androgen receptor signaling persists.^{1,4}

KEY STEPS IN THE ANDROGEN RECEPTOR SIGNALING PATHWAY^{1,4}

Key steps include androgen production, androgen binding, nuclear translocation, and DNA binding and transcription of tumor growth genes.



DISRUPTION BY HORMONE THERAPY^{2,3,8,10-20}

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MULTIPLE SCLEROSIS

Current Management Issues in Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic, disabling, neurological disease that affects the central nervous system (CNS), made up of the brain, spinal cord, and optic nerves.¹ In the United States, approximately 400,000 persons have MS; this equates to 200 new MS diagnoses every week.²

Multiple sclerosis is divided into four subtypes based on the clinical course of the disease.³ Approximately 80 to 85 percent of MS patients are diagnosed with relapsing-remitting MS (RRMS) at the time of diagnosis. This disease course is characterized by clearly defined acute attacks with full recovery or with residual deficit upon recovery. Secondary-progressive MS (SPMS) initially begins with RRMS, followed by progression of disability that may include minor plateaus and remissions. It can be characterized by less recovery following attacks, persistently worsening functioning during and between attacks, and/or fewer and fewer attacks (or none at all), accompanied by progressive disability. According to natural history studies, of the 80 percent of patients who start with RRMS, more than 50 percent will develop SPMS within 10 years; 90 percent will develop SPMS within 25 years.¹ Difficulty remains in the diagnosis of SPMS, and the date of SPMS onset is usually defined retrospectively once the duration of continuous neurological worsening has been established.⁴

Though there is no cure for MS, effective treatment exists for RRMS that may modify the disease course, treat exacerbations, manage symptoms, and improve function and quality of life. Disease modifying drugs (DMDs) are the mainstay of treatment for patients with both clinically diagnosed MS and a clinically isolated syndrome (CIS) with risk of MS development. Additionally, short courses of corticosteroids play an important role in the treatment of exacerbations and can shorten the duration and severity of attacks. The National Multiple Sclerosis Society (NMSS) issued an expert opinion consensus statement that emphasized the importance of initiating treatment



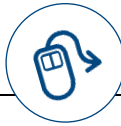
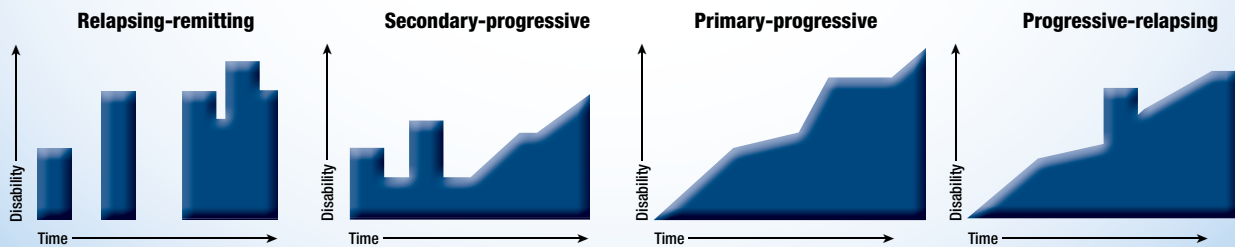


Table
1

Multiple Sclerosis: Disease Course and Frequency

Type	Frequency	Characteristics
Relapsing-Remitting MS (RRMS)	<ul style="list-style-type: none"> Accounts for 85% of cases at initial diagnosis 	<ul style="list-style-type: none"> Discrete attacks that evolve over days to weeks Attacks followed by some degree of recovery over weeks to months Patient has no worsening neurological function between attacks
Secondary-Progressive MS (SPMS)	<ul style="list-style-type: none"> Without DMDs, half of RRMS patients transition to SPMS within 10 to 20 years 	<ul style="list-style-type: none"> Initial relapsing course, followed by steadily worsening disease course Worsening disease may or may not have flare-ups/acute attacks
Primary-Progressive MS (PPMS)	<ul style="list-style-type: none"> Approximately 10% of patients are diagnosed with PPMS 	<ul style="list-style-type: none"> Steady decline in function from onset of disease No distinct relapses
Progressive-Relapsing MS (PRMS)	<ul style="list-style-type: none"> Relatively rare Approximately 5% of patients 	<ul style="list-style-type: none"> Steady functional decline from onset of disease Later superimposed acute attacks with or without recovery PRMS and PPMS cannot be distinguished during early stages

Source: MS Trend Report, NMSS, Loma, Lublin, et al.



Source: Lublin FD, et al. *Neurology*. 1996;46:907-911.

with DMDs. Currently, there are eight approved DMDs with an indication for MS treatment, with numerous oral and injectable DMDs on the horizon.

The treatment paradigm for MS is rapidly expanding, with a multitude of new DMDs expected in the next three years, providing neurologists additional options for therapy management. Though guidelines are available for MS treatment, the topics covered between the three major guiding MS organizations, including the American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), and National Institute of Clinical Excellence (NICE), hold significant variation and may be outdated in the near future.⁶

From the health plan perspective, the cost of DMD therapy is a concern as the currently available DMDs increased significantly in price from when these products were first launched. The average wholesale price (AWP) has increased by more than 11 percent on average between

2010 and 2011. Between 2009 and 2010, AWP per unit saw an increase of more than 16 percent and greater than 18 percent in 2008. This price increase outpaces the average inflation of all brand-name drugs, which saw a 9.4 percent increase in 2010.⁷ Much of the impact of MS to a health plan touches on the pharmacy budget. A health plan with approximately 1 million lives may see a cost of \$50 million per year for DMD spend,⁸ which is a cost that can be expected to increase in the next 10 years.

A recent analysis identified the total direct costs of MS to be approximately \$25,000 per patient per year; when adding in indirect cost measures (such as productivity losses and informal care), this figure increases to more than \$35,000. Interestingly, this analysis also compared patients with a recent relapse versus those who were clinically stable. The results showed that patients with a recent relapse cost approximately \$10,000 more (\$38,458 vs. 28,669; $p = 0.0004$), much of which was related to

MULTIPLE SCLEROSIS *continued*

	Identification	Causation	Alleviation	Prevention
Fatigue	Lack of physical or mental energy sufficient to limit activity	Primary MS, disease process Secondary to: medication, effort to overcome physical limitations, environmental influences, sleep disturbances, deconditioning, depression, comorbid diseases	Energy conservation Mobility aids Temperature control Drug therapies Treatment of comorbid conditions	Conditioning programs Good sleep hygiene Diet and weight control Discontinuation of smoking
Cognitive	Diminution in: -executive function -information processing -recall memory -sustained attention	MS disease process Secondary: -fatigue -drug therapy -depression -comorbid diseases	Treat fatigue, depression Sleep hygiene Limit sedative drugs Modify environment Anticholinesterases	Regular screening Modify activities to reduce risk of injury Adjust disease-modifying therapy
Mobility	Decreased endurance Fear of falls/recurrent falls Stiffness Weakness	Weakness Spasticity Ataxia Fatigability Pain Altered gait mechanics Comorbid diseases	Treat spasticity, fatigue Conditioning programs Adaptive exercises Orthotics Stabilizers Scooters	Early intervention to maintain posture/normal gait mechanics Conditioning programs Transfer training
Bladder dysfunction	Urgency, frequency Incontinence Incomplete emptying Need for manual pressure or straining to empty bladder	MS lesions in spinal cord Secondary -medication effects -comorbid conditions	Pharmacologic therapy Crede maneuver Intermittent catheterization Botulinum toxin injection Intranasal DDAVP	Adequate fluid intake Acidification of the urine Catheterization technique Monitor for incomplete emptying with PVR measurements

MS = multiple sclerosis; DDAVP = desmopressin acetate.

Source: Cohen B. Identification, causation, alleviation, and prevention of complications (ICAP). An approach to symptom and disability management in multiple sclerosis. *Neurology*. 2008;71(Suppl 3):S14–S20.

hospitalization.⁹ As noted in this study, MS has a substantial impact on both a health plan's pharmacy and medical benefits with MS relapses, resulting in an increase in costs due to hospitalizations, acute medications, and ambulatory care.⁹ Managed care organizations have a need to develop strategies to appropriately manage both the pharmacy and medical costs generated from this disease state while simultaneously applying the values of patient-centered care to ensure the best possible outcomes for the MS patient.

Treatment Barriers

From the patient perspective, relapses negatively impact quality of life (QOL) and result in productivity loss, as well as significant transient disability. The need for additional care and outreach to MS patients is evident. MS patients experience significant barriers to their treatment and support and strategies help to overcome these barriers. Various factors across chronic diseases negatively impact adherence to therapy. Such is the case in MS. A patient-reported study on barriers to adherence revealed that of the 31 percent of MS patients who missed at least one dose of their medication: 38 percent did not feel like taking their DMD, 33 percent were tired of taking a DMD, 35 percent had memory issues, 27 percent were concerned

with side effects of injecting, and 18 percent thought it interfered with their daily life (as well as other barriers).¹⁰ These issues can be minimized through the use of disease management programs that incorporate outreach by pharmacists and nurses. Disease management programs in MS have been shown to improve adherence, MS-related hospitalization, patient satisfaction, and the ability of a patient to manage his or her own health.^{11,12}

By using a more global approach for the management of MS patients, healthcare practitioners (HCPs) can take into consideration the impact of MS on a patient's daily life and provide more comprehensive care. One suggested method is the identification, causation, alleviation, and prevention of complications (ICAP) approach. This approach involves interpretation of information from MS patients about symptoms; determination of the cause; alleviation of symptoms, including comorbidities or factors that might worsen symptoms; and the proactive prevention of worsening and secondary effects.¹³ This method emphasizes consideration of the impact and consequences of symptoms from a short- and long-term perspective and encompasses comprehensive assessment and attention to the mitigation of symptoms and disability.

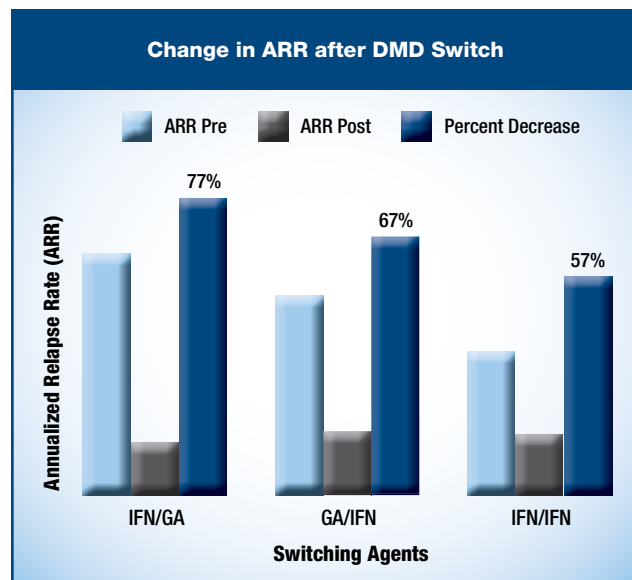
Treatment for MS should be individualized to meet

the specific needs of a patient, making it difficult for a strict treatment algorithm to be in place. However, there is a need to build consensus around a common approach to MS that allows for individual variation in therapy. This is important to ensure that patients are treated safely, effectively, and in a way that minimizes waste when drugs may no longer be working. A starting point for such an approach should focus on the use of platform therapy with interferon or glatiramer acetate as first-line treatment.¹⁴⁻¹⁸ These agents have more than 15 years of experience in the MS population, and the long-term effects of these agents are generally well known. Furthermore, consensus exists that platform therapy with higher-dosed/high-frequency interferon has shown improved efficacy over low-dose interferon without a substantial increase in adverse effects, yet there still appears to be significant treatment variability.^{19,20}

Patient Monitoring

The timely switch of MS patients to alternate agents and the adequate amount of time to leave a patient on therapy prior to a DMD switch is a concern for both neurologists and health plans alike. A question that comes up is what are the most appropriate methods for monitoring a patient in clinical practice, and when do you identify a patient as a non-responder? Varying definitions exist for patients that are non-responders across clinical trials, and the proportion of non-responders varies depending on the definition used.²¹ Although there is no consensus on the most appropriate method, studies have identified the importance of utilizing the expanded disability status scale (EDSS) in combination with MRI monitoring in routine clinical practice. Using a combination of EDSS and MRI has been shown to identify the presence of potentially poor response to therapy and to predict treatment response in the second and third years of therapy.²² Another potential option for monitoring MS patients in clinical practice is the use of patient-reported outcomes (PROs), such as the Multiple Sclerosis Impact Scale (MSIS-29), or a quality of life (QOL) tool, such as the MSQOL-54. Administration of PRO tools such as these prior to office visits allows for an important piece of tertiary information that can be tracked over time and provide the clinician information that may be missed at a regular office visit.²³⁻²⁵

Timely switching of MS therapy based on appropriate monitoring is important; however, limited guidance exists on switching of DMDs. One study found that patients that switched from interferon to glatiramer acetate had a 77



Source: Carrá A, Onaha P, Luetic G, et al. *Eur J Neurol*. 2008;15(4):386-393.

percent reduction in annualized relapse rate (ARR), those that switched from glatiramer acetate to interferon had a 67 percent reduction in ARR, and low-dose interferon to high-dose interferon groups saw a decrease of 57 percent.²⁶ Timely switching between these agents provides a potential benefit in relapse reduction and can eliminate use of a drug when it may no longer be effective. Additional options include switching to natalizumab or fingolimod, though both of these agents hold potential safety concerns. Natalizumab is an effective immunomodulator treatment for MS; however, treatment has been associated with a rare opportunistic infection: progressive multifocal leukoencephalopathy (PML). Recently, risk stratification algorithms were developed to minimize the risk of PML development by incorporating JC virus (JCV) antibody testing, allowing neurologists a safer approach to use natalizumab as a potential second-line option.²⁷ Much is still unknown about the safety of the immunosuppressant fingolimod in the treatment of MS. A U.S. Food and Drug Administration *MedWatch Report* cited serious adverse event report signals, such as cardiac-related issues, infection, and eye-related adverse effects indicating that safety concerns exist with this drug.²⁸

Clinical Pathway Programs

The current landscape of MS management is not so different from other disease areas, such as rheumatoid arthritis and oncology. Patient education, adherence to treatment, need for appropriate monitoring, and

MULTIPLE SCLEROSIS *continued*

rising costs of therapy are similar issues that face rheumatologists and oncologists. To alleviate these issues in other disease states, health plans have employed clinical pathway programs. Clinical pathways are structured, multidisciplinary approaches for delivering care to patients. They incorporate evidence-based processes and standardize a way that a MCO's network physicians and other healthcare providers treat a disease. Pathways encourage regular patient monitoring and provide patients with additional access to healthcare practitioners (HCPs). Although they may narrow treatment options, pathways still allow for individualized patient care and physician judgment while controlling the cost of care.

An exciting pipeline awaits the treatment of MS. There

are numerous novel agents that offer potential treatment options for patients who are unsuccessfully controlled with currently available DMDs. However, it is necessary to exercise caution with newer therapies, as they may hold potential safety risks that have not been identified in clinical trials. The current platform therapies have successfully treated MS patients for more than 15 years. Lastly, in this new era, the importance of providing resources such as disease management and individualized care management cannot be overstated. The development of a clinical pathway that encompasses patient-centered care, incorporates evidence-based practices for care delivery, and includes opportunities for cost-savings for health plans may be an important next step in the management of MS.

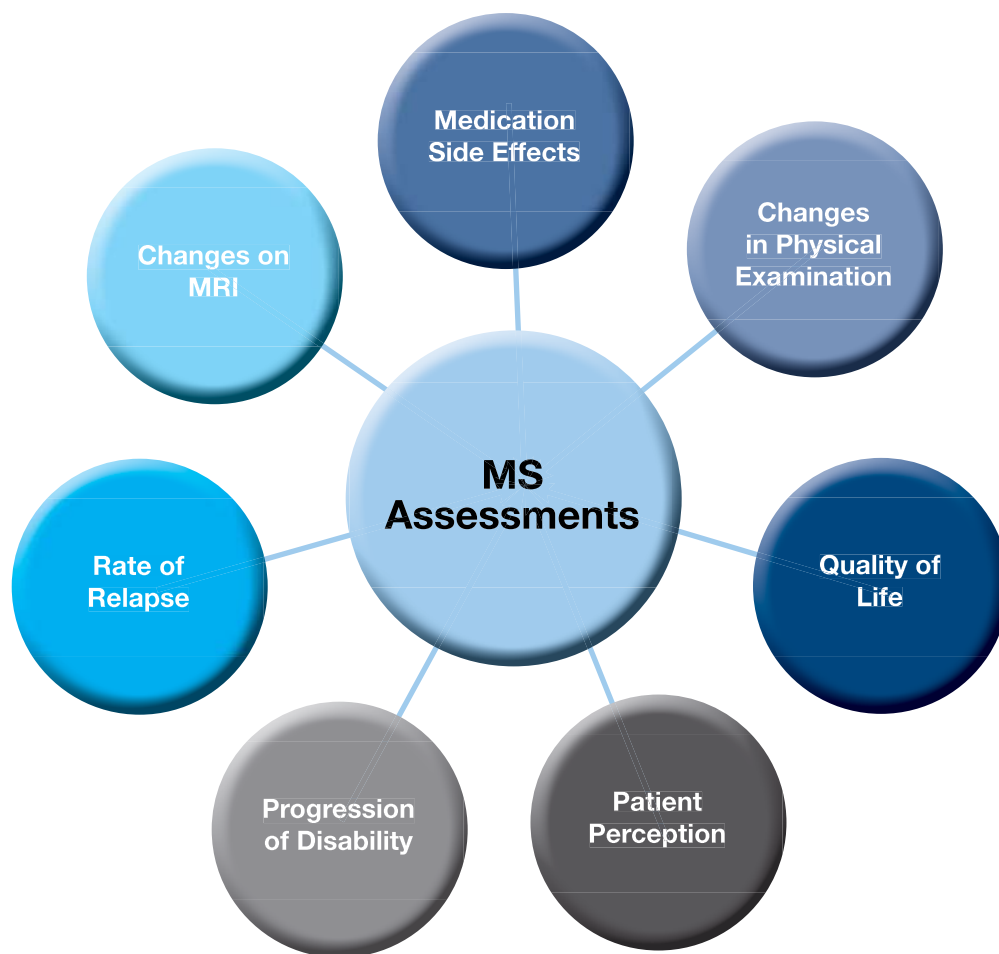


Table
2Disease Modifying Drugs for the Treatment of Multiple Sclerosis⁵

Agent	Dose and route of administration	Frequency of administration	Pharmaceutical company	Year of approval
Interferon β -1b SC (Betaseron [®])	250 μ g SC	Every other day	Bayer Pharmaceuticals	1993
Interferon β -1a IM (Avonex [®])	30 μ g IM	Once a week	Biogen Idec	1996
Glatiramer acetate (Copaxone [®])	20 mg SC	Daily	TEVA Pharmaceuticals	1997
Mitoxantrone (Novantrone [®])	Variable but usually 12 mg/m ²	Every 3 months up to a cumulative dose of 140 mg/m ²	EMD Serono	2000
Interferon β -1a SC (Rebif [®])	44 μ g SC	Three times per week	EMD Serono	2002
Natalizumab (Tysabri [®])	300 mg IV	Every 4 weeks	Biogen Idec	2006
Interferon β -1b SC (Extavia [®])	250 μ g SC	Every other day	Novartis Pharmaceuticals	2009
Fingolimod (Gilenya [®])	0.5 mg orally	Daily	Novartis Pharmaceuticals	2010

Source: Perumal J et al. Emerging disease-modifying therapies in multiple sclerosis. *Current Treatment Options in Neurology*. 2012;14:256-263.

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Managing Rheumatoid Arthritis: A Payor Perspective

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Horizon Blue Cross Blue Shield; and Daria I. Grisanzio, PharmD

Rheumatoid arthritis (RA) affects about 1.5 million adults (≥ 18 years) in the United States with a prevalence of approximately 0.5 to 1 percent.^{1,2} These patients bear a higher risk of morbidity and mortality than the general population. Among the most common co-morbidities in patients with RA are cardiovascular disease, infections, anxiety, depression, and lymphoproliferative malignancies.¹ The detrimental impact of RA extends beyond the physical and mental well-being of patients, resulting in societal effects. The costs associated with RA—both direct and indirect—can be extensive. In a report issued by the Centers for Disease Control and Prevention (CDC), the 2003 total direct and indirect cost of arthritis and other rheumatic conditions in the United States was estimated at \$128 billion.³ RA patients incurred healthcare expenditures several times greater than non-RA patients, with \$9,417 and \$3,159 mean cost per patient, respectively, in 2006.⁴ Over the past decade, RA has consistently been one of the most expensive disease states in the United States.⁴ Additionally, during this time frame, the overall cost of RA prescription medications has increased substantially.⁴ Indirect work-related costs for this patient population, which has an employment rate of only approximately 30 to 60 percent, include both absenteeism and presenteeism.⁴⁻⁶



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Clinical Guideline Update

In 2012, an update to the 2008 American College of Rheumatology (ACR) recommendations for the use of disease-modifying antirheumatic drugs (DMARDs) in patients with RA was published. DMARDs are the cornerstone of RA treatment and have been shown to slow joint damage and disease progression. The 2012 update placed emphasis on early therapy initiation and aggressive treatment, due to the belief that this may further help prevent irreversible damage and result in better outcomes for the patient and for society as a whole. The update focused on indications for non-biologic as well as biologic DMARDs; when to switch or change therapies; use in patients with hepatitis, congestive heart failure (CHF), and malignancy; when to screen for tuberculosis (TB); and vaccine administration. ACR sought to update these guidelines to include newly marketed therapeutic agents (tocilizumab [Actemra®], certolizumab pegol [Cimzia®], and golimumab [Simponi®]) and to streamline the recommended treatment algorithm while taking into account current and, in some cases, growing concerns in the care of these patients. As previously stated, RA patients carry a high risk for infection, which



is further increased in the use of biologic agents. It should be noted that while a new classification system for RA was published in 2010, the 2012 guideline update used the previous RA classification system due to the end date used in the literature search.⁷

The guidelines recommend early initiation (disease duration of less than six months) of DMARD monotherapy in patients with low disease activity and moderate/high disease activity without poor prognostic factors; hydroxychloroquine [Plaquenil®] with methotrexate [Trexall™, Rheumatrex®] is also an option for these high activity patients. For the moderate/high activity patients with poor prognostic factors, early DMARD combination therapy (with or without methotrexate) is recommended. Anti-tumor necrosis factor (TNF) agents are also an option for patients with high disease activity and poor prognosis. In patients with established disease (duration greater than or equal to six months or meeting 1987 ACR classification), DMARD monotherapy is recommended for low activity patients without poor prognostic factors, while those with poor prognostic factors and moderate/high patients are recommended methotrexate monotherapy or DMARD combination therapy (Table 1).⁷

Recommendations were also made for initiation and switching of DMARD therapy in patients with deteriorating conditions after three months of therapy. For moderate/high activity patients, switching from oral DMARDs to biologics or adding a biologic may be recommended. When a moderate/high activity patient experiences a lack or loss of benefit to an anti- or non-TNF biologic, he or she may switch to another anti- or non-TNF agent. In cases of biologic treatment failure after an adverse event, patients may switch to an anti- or non-TNF agent, depending on the disease activity and event severity.⁷

The recommendations for patients with hepatitis, malignancies, and CHF vary depending upon factors such as disease type and severity. In addition, all patients should be screened for latent TB if treatment with a biologic agent is considered. Diagnostic follow-up, treatment, and annual rescreening should be performed when appropriate. Immunization guidelines should be followed and all recommended vaccinations (including herpes zoster vaccine [Zostavax®]) administered prior to therapy initiation or in cases where prior vaccinations were missed.⁷

Table
1

2012 ACR Guideline Initial Treatment Recommendations by Disease Activity and Severity

	DMARD Mono	DMARD Combo	Anti-TNF +/- MTX	HCQ + MTX	MTX
Early RA					
Low	x				
Moderate					
No PPF	x				
PPF		x			
High					
No PPF	x			x	
PPF		x	x		
Established RA					
Low					
No PPF	x				
PPF		x			x
Moderate/High		x			x

*Table provides initial treatment options, but these may vary depending upon patient's current medications. Anti-TNF = Anti-tumor necrosis factor agent; Combo = Combination therapy; DMARD = Disease-modifying antirheumatic agent (hydroxychloroquine, leflunomide, methotrexate, minocycline, or sulfasalazine); Early = Disease duration < 6 months; Established = Disease duration ≥ 6 months or meeting 1987 ACR classification criteria; HCQ = Hydroxychloroquine; MTX = Methotrexate; Mono = Monotherapy; PPF = Poor prognostic factors; RA = Rheumatoid arthritis.

Table
2

Comparison Chart of Biologics

Product	Indication	Benefit Coverage	Initial U.S. Approval
Abatacept (Orencia®)	Adults with moderate-to-severe RA	Medical (IV) Pharmacy (SQ)	2005 2011
Adalimumab (Humira®)	Adults with moderate-to-severe RA	Pharmacy	2002
Certolizumab pegol (Cimzia®)	Adults with moderate-to-severe RA	Pharmacy	2008
Etanercept (Enbrel®)	Moderate-to-severe RA	Pharmacy	1998
Golimumab (Simponi®)	Adults with moderate-to-severe RA in combination with MTX	Pharmacy	2009
Infliximab (Remicade®)	Moderate-to-severe RA in combination with MTX	Medical	1998
Rituximab (Rituxan®)	Adults with moderate-to-severe RA with inadequate response to ≥1 anti-TNF agent, in combination with MTX	Medical	1997 (for RA in 2006)
Tocilizumab (Actemra®)	Adults with moderate-to-severe RA with inadequate response to ≥1 anti-TNF agent	Medical	2010

Cost and Utilization of RA Treatment

As previously noted, the costs associated with RA can be extensive. Studies have examined the costs and utilization associated with RA from a payor perspective. In an analysis of 2003 claims data for West Virginia Medicaid RA patients, \$2,054,470 was paid by the plan for RA medication claims. These prescription claims totaled 74.6 percent of the total cost expenditures paid out for these patients with another \$698,480 spent on medical services. Only approximately 40 percent of these RA patients received a DMARD and 12.4 percent received a biologic, with biologics carrying the highest portion of the prescription costs. Of the RA patients in this population, 79.3 percent had prescription claims from two or more drug categories (DMARDs, biologics, non-steroidal anti-inflammatories (NSAIDs), oral steroids, and narcotic analgesics) and, of this, 60.1 percent had claims from three or more of the categories.⁸

DMARD Initiation in Early RA

Despite the recommendation for early DMARD therapy, studies have shown that many RA patients are not receiving appropriate treatment.^{2,8,9} One study, using commercial and Medicare coordination of benefits (COB) databases from 2003 to 2009, found that DMARD treatment had not been initiated within the first year of diagnosis for 37 percent of these patients. Of the 63 percent of patients who received a DMARD, only 87 percent filled a

prescription within three months and another 8 percent within three to nine months of diagnosis. Compared to patients who had initiated DMARD therapy, patients who had not initiated DMARD treatment tended to have significantly higher healthcare expenditures (\$10,534 vs. \$12,725, respectively), pharmacy drug costs (\$2,438 vs. \$2,822, respectively), and use a greater amount of healthcare services.² Patients in whom early DMARD therapy was initiated had a lower rate of hospitalizations than those in whom early therapy was not initiated (12.7 percent vs. 18.6 percent, respectively).²

DMARD Impact on Star Ratings

Another study examined the Healthcare Effectiveness Data and Information Set (HEDIS) RA measure of DMARD prescription fills (at least one fill per reporting year) for Medicare claims for services rendered between 2005 and 2008. The patient population in this study included both newly and previously diagnosed RA patients. Analyses showed that only 63 percent of the RA patients included received a DMARD, and identified specific groups of patients that were at a lower rate of receipt. Wide variation existed (16 to 87 percent) on the rate, dependent upon the plan, thereby leaving significant room for improvement.⁹ One method for increasing adherence to the guidelines and the percentage of patients receiving appropriate DMARD therapy is to focus on the plan's RA Star Rating metric, measure C22 from the Centers for Medicare &

Medicaid Services (CMS) Quality and Performance Ratings for 2012.¹⁰ This measure rates plans on a five-star scale (with a four-star threshold of ≥ 78 percent) for the percentage of plan members with RA who received at least one ambulatory prescription for a DMARD during the reporting year.¹⁰ Managed care organizations can improve their Star Rating for this measure by monitoring patients with a diagnosis of RA who are not receiving a DMARD and intervening appropriately. Plans may see improved patient outcomes due to an increase in adherence to best practice guidelines.

Many publications exist on the benefits of DMARD use in RA patients, including studies that have shown the use of DMARDs and biologic agents in early RA results in improved clinical outcomes. Studies also indicate that early, aggressive DMARD treatment results in decreased absenteeism, decreased presenteeism, decreased job loss, and increased work productivity.¹¹⁻¹³ Patients receiving a biologic for early RA were also more likely to see improvement in their well-being and in their ability to work, if work was available.¹⁴ By focusing on the Star Ratings metric, managed care organizations can help to maintain this improvement. Decreased time away from work and increased productivity correlates to lower healthcare expenditures for these patients. For managed care organizations, increased Star Ratings means eligibility for greater reimbursements and bonuses from CMS.

Strategies for Improvement

While initial treatment with an oral DMARD is an appropriate and highly cost-effective strategy, estimates from the payor perspective indicate that first-line early RA treatment with a biologic may also be cost-effective.¹⁵ The clinical benefits seen from early biologic initiation may help drive formulary changes, as to which product may be first- versus second-line therapy. Formulary management of biologics may be able to help offset the higher cost of these medications^{8,16} since plans have the option to select between self-injectable or infusible biologics and may be able to negotiate with drug companies for better pricing. Lower costs to the patient may translate to increased compliance and, in turn, decreased utilization of medical services and lower healthcare expenditures.¹⁵ Reinforcing adherence to treatment guidelines through educating practitioners and specialty pharmacies to monitor for adverse reactions and events, particularly with biologics, is critical.

The quality of care received by patients is at stake when the guidelines, which constitute best practices, are

not followed. By driving adherence to the guidelines and initiating early DMARD therapy (within three months of diagnosis), benefits may be achieved for the well-being of the patients as well as for society and payor organizations. As previously shown,² a significant cost and utilization disparity exists which, if minimized, may help to contain expenditures, such as those incurred by inpatient and outpatient medical services. There is room for improvement in the areas of increased patient follow-up and the administration of proper treatment. Patients should be periodically reevaluated every three to six months, at which point practitioners should monitor for clinical improvement, lack of deterioration, and presence of adverse reactions. Many RA patients are prescribed ancillary analgesics, including narcotic medications; increased use of these medications may indicate that the patient's disease is not being properly managed and treatment adjustments need to be made. Follow-up of this information by payor organizations will help to ensure a high quality of patient care.

Specialty pharmacies, as well as practitioners, have the ability to make an impact in this area. These pharmacies can move beyond a dispensing role and act as a liaison between the patient, practitioner, and payor. By virtue of being able to see what medications these patients are filling, when, and in what doses, specialty pharmacies are able to monitor compliance (e.g., missed doses or fills), disease progression, presence of adverse reactions, and whether there is a need to change therapy.

Managed care organizations and industry manufacturers can help in this process by educating practitioners on how to recognize, correctly diagnose, and treat RA. Many times, the first practitioner to see these patients is an internist or primary care physician. Training these practitioners to recognize the differences between RA and other diagnoses and when to refer patients to a specialist will help to increase the number of patients receiving proper treatment as early as possible. This, in turn, will help to decrease costs and minimize the amount of irreversible disease progression-related damage.

One of the biggest challenges for plans is managing the site of administration for RA medications for these patients because it may fall under medical and not pharmacy benefits. While medications such as etanercept (Enbrel®) and adalimumab (Humira®) are self-injectable and can be dispensed through pharmacies, others, such as infliximab (Remicade®) and abatacept (Orencia® IV), are infused and need to be administered in a physician's office or other facility (Table 2). These administration considerations for

infused medications, which also have dosing limits and infusion intervals, can result in increased costs, especially if administered in a hospital setting. Irrespective of whether a patient has medical and/or pharmacy benefits, the most appropriate treatment and site of administration needs to be selected. Payor organizations should have in place prior authorization (PA) and utilization management (UM) processes for the denial of inappropriate use or dosing of these medications.

A comprehensive approach that payors can utilize to address these clinical and financial barriers is to implement clinical pathways of care. Several payor organizations throughout the country are beginning to develop clinically sound and cost-effective pathways designed to improve the overall care provided to patients with RA. These pathways focus on routine monitoring, low-cost infusion sites, and adherence to dosing guidelines. While providers are not mandated to strictly follow these pathways, those practitioners who demonstrate a high compliance rate may receive a positive adjustment in their reimbursement. In addition, physicians are compensated for cognitive services, such as comprehensive patient evaluations and prudent monitoring. Incentivizing providers has proven to be a useful tool in the implementation of clinical pathways and greatly minimizes pushback while improving the standard of care.

Anticipating the Arrival of Biosimilars

Looking ahead, the arrival of biosimilar DMARDs to the market in the near future may result in further changes for managing formularies and patient care. Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration have issued guidance for the development of biosimilars, and several companies have products in various stages of clinical research. The question is what effect these products will have once they reach the market. Providers and managed care organizations will need to examine the indications, safety data, and efficacy profiles to help select the best treatment and cost-effective options. While the size of the economic impact is unknown, there exists the potential to significantly decrease costs by an estimated 20 to 30 percent.¹⁷

The care of patients with RA poses a challenge for managed care. The costs associated with this disease can be significant and affect patients, providers, and payors. Managed care organizations can help to ensure appropriate treatment of these patients and, in turn, decrease costs. Monitoring of parameters,

such as selection of appropriate early DMARD therapy, concomitant methotrexate administration, or presence of adverse events will give payors the opportunity to target areas for improvement, which can be seen in HEDIS and Star Rating measures. Educating practitioners and specialty pharmacies to assist in the process can help result in better outcomes. These factors, combined with selecting appropriate treatment and administration sites, and PA/UM processes, will help effectively manage treatment and costs for these patients.

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Cost Containment in a New Era of Hepatitis C Treatment

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The Burden of HCV Infection

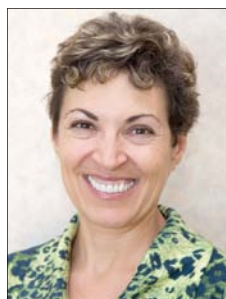
Hepatitis C virus (HCV) continues to be the most common chronic blood-borne illness in the United States.¹ Although the incidence of HCV has decreased since the early 1990s, there are an estimated 2.7 to 3.9 million Americans who remain chronically infected.^{2,3} Harder-to-treat HCV genotypes 1a and 1b continue to make up 73 percent of all HCV infections.⁴ It has been estimated that cirrhosis develops in 25 to 30 percent of patients infected with HCV, which complicates the treatment process.⁵ Additionally, more than 25 percent of cirrhotic patients will develop end-stage liver disease or hepatocellular carcinoma, with liver transplantation being the only life-saving therapy.⁵

Given these statistics, it is not surprising that HCV is the most common indication for adult liver transplantation in the United States.⁶ Regardless of disease severity, it is important that all patients with HCV are appropriately evaluated for treatment, as precirrhotic HCV infection is not a benign condition; multiple organ systems are affected by the virus and HCV infection has been associated with steatosis, diabetes, kidney disease, and certain lymphomas, among other sequelae.⁵

Direct medical costs in the United States associated with chronic HCV infection are estimated at up to \$1.66 billion annually.²¹ However, indirect medical costs have been estimated at two times the direct medical costs.²² In a model by Wong et al, the U.S. societal costs for premature mortality for patients younger than 65 years with HCV is estimated to be \$54.2 billion from 2010 through 2019.²³ Costs of morbidity due to disability from decompensated cirrhosis and hepatocellular carcinoma were estimated to be \$21.3 billion for the same time period.²³ Furthermore, it was projected that direct medical expenditures for HCV would increase by \$10.7 billion, despite a stable disease rate.²³

The Advent of Triple Therapy

Early on, clinicians relied on standard interferon alpha to treat HCV infection. However, in the late 1990s, pegylated interferon alpha combined with ribavirin used for at least 48 weeks became the standard of care, as it led to significant improvements in sustained viral response (SVR).⁷ Despite this advance, the cure rate for treatment-naïve individuals with genotype-1 remained around 40 to 50 percent, with even worse outcomes for certain subgroups, such as patients with prior treatment failure or cirrhosis and patients with



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human immunodeficiency virus co-infection.⁸

In 2011, the U.S. Food and Drug Administration (FDA) approval of boceprevir (Victrelis®; Merck & Co., Inc.) and telaprevir (Incivek®; Vertex Pharmaceuticals, Inc.) marked a new era in the treatment of HCV infection.^{9,10} Both of these agents, known as direct-acting NS3/4A protease inhibitors, have

demonstrated significantly higher rates of SVR as add-on therapy to pegylated interferon alpha and ribavirin compared with the standard of care, dual therapy with pegylated interferon alpha and ribavirin. These agents proved effective in both treatment-naïve and treatment-experienced patients with genotype 1.¹¹⁻¹⁵ SVR rates of up to 75 percent were observed for treatment-naïve patients¹¹ and SVR rates of up to 83 percent were observed in prior relapsers.¹² Triple drug therapy with the addition of a protease inhibitor also demonstrated a reduced lifetime risk of hepatocellular carcinoma by up to 38 percent and was associated with an increased quality-adjusted life expectancy.²⁴ Furthermore, these agents have allowed response-guided therapy to be utilized, allowing shorter treatment duration in the large amount of patients who have rapid virologic response.⁸ Boceprevir and telaprevir have since become the new standard of care and have been incorporated into major U.S. guidelines for HCV treatment.¹⁶

Boceprevir vs. Telaprevir

There are some significant differences between telaprevir and boceprevir that are important to recognize from a pharmacoeconomic perspective. Treatment with telaprevir requires two tablets to be taken three times daily for 12 weeks in all patients.¹⁰ Treatment with boceprevir requires four tablets to be taken three times daily for 24 to 44 weeks.⁹ While the duration of treatment with boceprevir is guided by the virologic response to therapy, the duration of telaprevir is consistent for all patients regardless of response.¹⁰ Treatment with boceprevir, although seemingly more complicated, allows physicians to tailor the duration of triple drug therapy based on their specific patients' viral response.⁹ The cost of these competing agents

is another differentiating factor. The wholesale acquisition cost (WAC) for 12 weeks of telaprevir is \$52,644 per patient.¹⁷ The WAC for boceprevir is lower and ranges from \$28,248 for 24 weeks to \$51,788 for 44 weeks of therapy.¹⁷ These costs are all in addition to dual therapy with pegylated interferon alpha and ribavirin, which can be more than \$60,000, depending on the products prescribed.

Head-to-head trials have not been conducted comparing the two available protease inhibitors, but both agents seem to show similar efficacy results in clinical trials. However, it is important to recognize that only telaprevir was studied and is approved for use in prior null responders.^{12,18} For treatment-naïve patients and patients with a delayed virologic response, rates of SVR were similar in patients who achieved a rapid virologic response after the initiation of protease inhibitor therapy.¹⁸ Additionally, a similar percentage of treatment-naïve patients who achieved a rapid virologic response could be treated for a shorter duration.¹⁸ When interleukin (IL)-28B status is considered, SVR rates also appear to be similar between agents.¹⁸

Based on cross-trial comparisons, it appears that telaprevir is associated with an elevated risk of rash and pruritis.¹⁹ Treatment-naïve patients treated with a response-guided boceprevir regimen appear to be more likely to develop neutropenia compared with patients treated with a response-guided telaprevir regimen.¹⁹ Anemia is a significant side effect of both agents and appears to have occurred at similar rates in both treatment groups.¹⁹ For patients who develop anemia, the cost of erythropoietin-stimulating agents (ESAs) is an important consideration, regardless of which protease inhibitor is being used.²⁰ Reducing the dose of ribavirin before initiating ESAs may be a cost-saving strategy that does not compromise treatment efficacy.²⁰

An indirect comparison of boceprevir and telaprevir trials revealed that discontinuation rates in treatment-naïve and treatment-experienced patients were similar between both agents.¹⁹ Boceprevir has a more complicated but less-expensive regimen, with a potentially better side effect profile compared with telaprevir, but the impact of these factors on medication adherence has not been established. Medication adherence is an important aspect of success with HCV treatment; however, published comparisons between these agents are lacking.

As more data become available for these novel agents, and as they undergo regulatory review and ultimately come to market, treatment of HCV infection and cure rates will undoubtedly improve. It is critical to rely on guidelines with clear start and stopping rules to maximize the potential clinical and economic value of cost/cure.

Medication Adherence and Its Cost Implications

Adherence to HCV treatment with pegylated interferon alpha and ribavirin is suboptimal; it has been estimated that 10 to 20 percent of patients will not complete therapy because of poor adherence and will discontinue due to tolerability and side effects.²⁵ Side effects of dual therapy include depression, fatigue, and flu-like symptoms, among others.²⁵ Furthermore, higher rates of substance abuse, psychiatric disorders, and cognitive impairment put patients with chronic HCV infection at a higher risk for poor medication adherence.²⁶ A recent study by Lo Re et al demonstrated the importance of adherence to HCV therapy to maximize virologic outcomes.²⁷ In this study that included more than 5,700 patients, early virologic response and sustained virologic response both increased with higher levels of adherence, as measured by pharmacy records.²⁷ It was also noted that adherence was highest in the first 12 weeks of therapy, but diminished thereafter.²⁷

It is important to recognize that triple therapy that includes either boceprevir or telaprevir has more side effects than dual therapy, and treatment with either agent results in a significant pill burden. Additionally, boceprevir and telaprevir need to be taken three times daily with food.^{9,10} It has been demonstrated in medication adherence studies that as dosing frequency increases, medication adherence decreases.²⁶ Treatment for HCV is time-limited, so different approaches to medication adherence should be taken than those utilized with other chronic conditions, such as HIV.²⁶ As demonstrated in a cost-effectiveness analysis of the new protease inhibitors, the cost per successful treatment increased dramatically when adherence to therapy decreased. The analysis showed that a 50 percent adherence rate to HCV regimens increased the cost per quality adjusted life year gained to as high as three times the acceptable level.

Medication adherence is a crucial consideration for managed care decision makers and payors to ensure that the success observed in the clinical trials of these new protease inhibitors translates into real-world outcomes. Patient pre-treatment assessment, as well as on-treatment medication adherence monitoring and support, are necessary to ensure success with these costly therapies.²⁶ There are multiple factors that affect medication adherence, such as out-of-pocket costs, poor coordination of care, health literacy, and side effects of medications.²⁸ However, integrated models that utilize nurses or clinical pharmacists to assess medication adherence and counsel patients have shown to not only increase medication adherence, but also decrease overall costs.²⁸

Genomic Testing and Personalized Medicine

There is a significant amount of unexplained variability in treatment response despite consideration of viral factors, such as genotype, and host factors, such as medication adherence. This may be explained by genetic factors that modulate response to standard HCV treatment. The use of genomic testing to personalize HCV therapy is a relatively recent phenomenon; however, it has the potential to be a cost-saving strategy.

IL-28B testing is recommended in the 2011 American Association for the Study of Liver Diseases hepatitis C treatment guidelines as a consideration when the patient or provider would like additional information on the probability of treatment response or on probable treatment duration that will be needed.¹⁶ Questions do remain, however, such as whether IL-28B genotype is more predictive of SVR versus early-on treatment response, and whether shortening duration of HCV treatment is feasible based on IL-28B genotype.³⁰

Table 1 Select Agents in the HCV Pipeline ³¹			
Drug Name	Drug Class	Company	Phase of Development
BI-201335	Protease inhibitor	Boehringer Ingelheim	Phase III
TMC-435	Protease inhibitor	Medivir/Tibotec	Phase III
ACH-1625	Protease inhibitor	Achillion	Phase II
Asunaprevir	Protease inhibitor	Bristol-Myers Squibb	Phase II
Danoprevir	Protease inhibitor	InterMune/Genentech	Phase II
MK-5172	Protease inhibitor	Merck	Phase II
Daclatasvir	NS5A inhibitor	Bristol-Myers Squibb	Phase III
GS-7977	Polymerase inhibitor	Gilead	Phase III
RG-7128 (mericitabine)	Polymerase inhibitor	Gilead/Genentech	Phase II
VX-222	Polymerase inhibitor	Vertex	Phase II

Another gene, inosine triphosphatase (ITPA), is of interest from a cost perspective. ITPA deficiency has been shown to increase the risk of ribavirin-induced anemia.²⁹ These preclinical findings have been reproduced in HIV/HCV co-infected patients who are at a greater risk of anemia and require higher doses of ESAs.²⁹ Although more studies are necessary, testing for ITPA deficiency may be a future consideration in predicting risk of anemia associated with ribavirin and managing ESA use.

Prospects for the Future

Although 2011 marked a new paradigm in HCV treatment with the approval of the first protease inhibitors, the pipeline of future agents is robust (Table 1).³¹ The ideal HCV treatment regimen would have a short duration and easy once-daily dosing with low pill burden; all-oral administration (replacing subcutaneous pegylated interferon alpha); high effectiveness in challenging populations, such as null responders and partial responders; efficaciousness in all genotypes; and, most important, safety and tolerability.

A second wave of first-generation NS3/4A protease inhibitors in clinical development may have improved efficacy and offer more convenient dosing, with potentially improved resistance profiles over boceprevir and telaprevir.

New agents in this class include TMC-435, BI-201335, and ACH-1625, all of which have once-daily dosing and are being evaluated in combination with pegylated interferon alpha and ribavirin.³² In addition, novel classes of agents, including nucleoside and non-nucleoside polymerase inhibitors, NS5A inhibitors, and cyclophilin inhibitors, are currently being tested in a variety of combinations and patient subtypes. Several of these agents are also being studied as interferon-free therapeutic options.^{33,34}

As more data become available for these novel agents, and as they undergo regulatory review and ultimately come to market, treatment of HCV infection and cure rates will undoubtedly improve. It is critical to rely on guidelines with clear start and stopping rules to maximize the potential clinical and economic value of cost/cure. The role of pharmacogenomics has evolved in HCV treatment and has not only been recommended by guidelines, but also has the potential to maximize the value of these high-cost therapies. It is also critical that managed care organizations focus on member support, innovative solutions, and best practices to ensure adherence and compliance to HCV therapies as a strategy to improve overall health outcomes, reduce the likelihood of viral resistance, limit the amount of medication waste, and reduce total healthcare expenditures.

Incremental cost-effectiveness of new protease inhibitors in HCV infection assuming IL-28B testing is unavailable²⁴

	MILD FIBROSIS	ADVANCED FIBROSIS
Boceprevir	\$70,100/QALY	\$36,300/QALY
Telaprevir	\$91,000/QALY	\$47,000/QALY

Incremental cost-effectiveness of new protease inhibitors in HCV infection if utilizing IL-28B-guided therapy²⁴

	MILD FIBROSIS	ADVANCED FIBROSIS
Boceprevir	\$62,900/QALY	\$32,800/QALY
Telaprevir	\$86,800/QALY	\$45,300/QALY

In this decision-analytic Markov model, the impact of adding telaprevir or boceprevir to dual therapy with pegylated interferon alpha and ribavirin in patients with HCV genotype 1 mono-infection was evaluated. The impact of IL-28B genotype testing was also studied. IL-28B testing may be predictive in determining patients most likely to benefit from a protease inhibitor. Either protease inhibitor was shown to be a cost-effective (incremental cost-effectiveness ratio [ICER] ≤\$50,000) addition to pegylated interferon alpha and ribavirin in patients with advanced fibrosis. Furthermore, IL-28B guided therapy lowered ICERs for both boceprevir and telaprevir.²⁴

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For your patients with type 2 diabetes who need more than
A1C control, choose Levemir® (insulin detemir [rDNA origin] injection)

24/7 GLUCOSE CONTROL



Karen's doctor said taking
Levemir® (insulin detemir [rDNA origin] injection)
once-daily may get her the control
she needs & more

Low rates of hypoglycemia

In 1 study, approximately 45% of patients in each treatment arm achieved **A1C <7% with no hypoglycemic events** within the last 4 weeks of observation.¹

- A single major hypoglycemic event was reported in the 70-90 mg/dL group; no major hypoglycemic events in the 80-110 mg/dL group
- Minor hypoglycemia rates were 5.09 (70-90 mg/dL) and 3.16 (80-110 mg/dL) per patient-year*

From a 20-week, randomized, controlled, multicenter, open-label, parallel-group, treat-to-target trial using a self-titration algorithm in insulin-naïve patients with type 2 diabetes, A1C $\geq 7\%$ and $\leq 9\%$ on OAD therapy randomized to Levemir® and OAD (1:1) to 2 different fasting plasma glucose (FPG) titration targets (70-90 mg/dL [n=121] or 80-110 mg/dL [n=122]). At study end, in the 80-110 mg/dL group, 55% of patients achieved goal (A1C <7%) with A1C decrease of 0.9%. The mean A1C was 7%.¹

Covered on more than 90% of managed care plans^{2†}

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

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

Do not dilute or mix Levemir® with any other insulin solution, or use in insulin infusion pumps. Do not administer Levemir® intravenously or intramuscularly because severe hypoglycemia can occur.

Hypoglycemia is the most common adverse reaction of insulin therapy, including Levemir®. The timing of

hypoglycemia usually reflects the time action profile of the administered insulin formulations. Glucose monitoring is essential for all patients receiving insulin therapy. Any changes to an insulin regimen should be made cautiously and only under medical supervision.

Needles and Levemir® FlexPen® must not be shared.

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®. Adverse reactions associated with Levemir® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash and pruritus. Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.

Levemir® has not been studied in children with type 2 diabetes, and in children with type 1 diabetes under the age of six.

Please see brief summary of Prescribing Information on adjacent page.

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

*Minor=SMPG <56 mg/dL and not requiring third-party assistance.

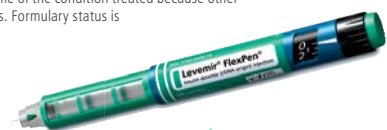
†Intended as a guide. Lower acquisition costs alone do not necessarily reflect a cost advantage in the outcome of the condition treated because other variables affect relative costs. Formulary status is subject to change.



On your iPhone®
Scan the QR code to download
the NovoDose™ app to know
how to optimally dose Levemir®

References: 1. Blonde L, Merilainen M, Karve V, Raskin P; TITRATE™ Study Group. Patient-directed titration for achieving glycemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE™ study. *Diabetes Obes Metab*. 2009;11(6):623-631. 2. Data on file. Novo Nordisk Inc, Princeton, NJ.

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Levemir® FlexPen®
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. 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.

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.

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

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

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

Table 4: Adverse reactions (excluding hypoglycemia) in a 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

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. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a blood glucose below 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (<50 mg/dL in Study A and C) that was self-treated by the patient. 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

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

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	
		Twice-Daily LEVEMIR®	Twice-Daily NPH	Once- or Twice Daily LEVEMIR®	Once- or Twice Daily NPH
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)
	Event/patient/year	0.01	0.08	0.04	0.13
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)
	Event/patient/year	3.5	6.9	1.6	2.0

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 lipatrophy (thinning of adipose tissue), and may affect insulin adsorption. 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, pruritis, 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.

More detailed information is available upon request.

For information about LEVEMIR® contact:

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Manufactured by:
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Revised: 1/2012

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LEVEMIR® is covered by US Patent Nos. 5,750,497, 5,866,538, 6,011,007, 6,869,930 and other patents pending.

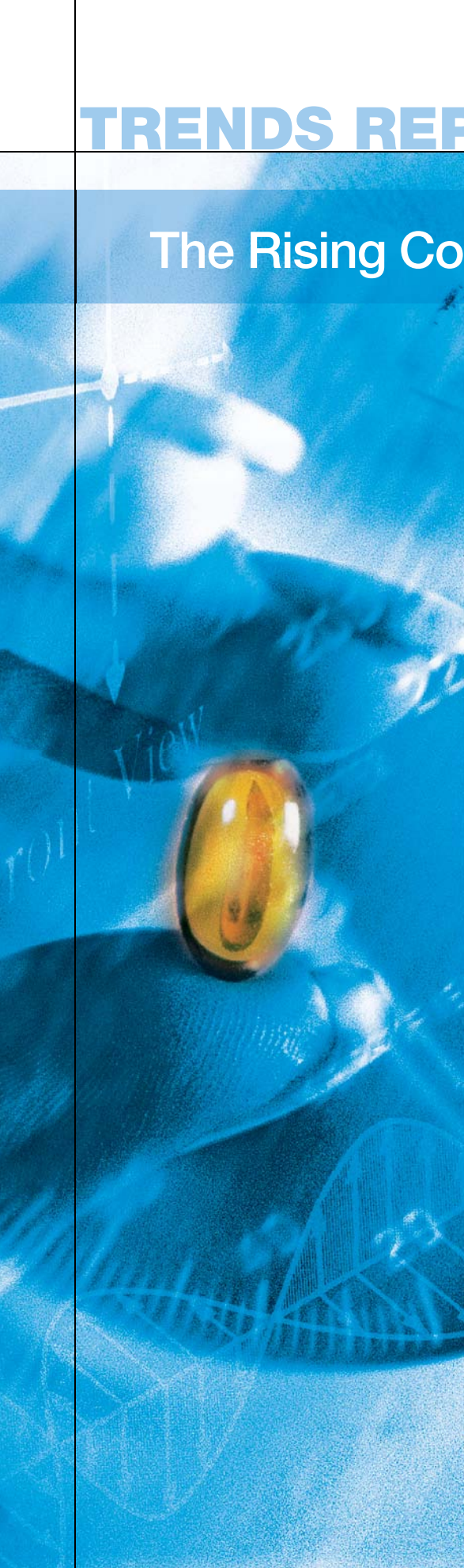
FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,400 and other patents pending.

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Levemir®
insulin detemir (rDNA origin) injection

The Rising Cost of Specialty Pharmaceuticals



The cost and utilization of specialty pharmaceuticals are increasing at an alarming rate. These are prescription medications used to treat complex medical conditions and generally require special handling or administration. Although only 1 percent of the U.S. population requires treatment with specialty pharmaceuticals, these medications account for nearly 18 percent of health plans' pharmacy-related budgets.¹ As this estimate takes into consideration only those claims captured under the members' pharmacy benefits, a large portion of the total expenditure—approximately 47 percent billed to the members' medical benefits—is often neglected during financial analyses. This presents a major barrier for health plans trying to develop cost-effective strategies to contain the escalating cost of specialty drugs.

In 2011, the average prescription price of specialty medications rose by more than 17 percent. This trend is expected to continue over the next several years. Early forecasts estimate that specialty medications will represent 40 percent of health plans' pharmacy expenditures by 2017.¹ The four specialty disease states that generate the highest financial burden are inflammatory conditions (e.g., rheumatoid arthritis), multiple sclerosis, cancer, and HIV. These conditions represent nearly 70 percent of the total specialty drug spend within commercial health plans' pharmacy benefits.¹

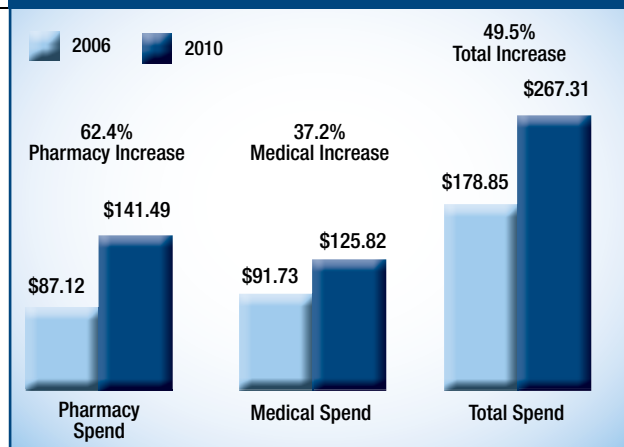
Specialty Management Challenges

A variety of factors are accelerating the specialty market. In disease states such as rheumatoid arthritis and multiple sclerosis, biologic medicines can help control disease severity and progression. However, these medications consume a large amount of financial resources and are becoming increasingly prevalent in practice, leading to double-digit percent growth. In addition, low competition and lack of generic options have allowed manufacturers to frequently increase the ingredient cost of specialty products.²

Although infused drugs have historically dominated the specialty market, pharmaceutical companies have been developing equally effective treatment options with alternate dosage forms for many specialty disease states. New oral therapies and self-injectables are allowing drugs to become more convenient and accessible to patients and prescribers. These new dosage forms are shifting the economic burden away from medical reimbursement and placing the financial responsibility within health plan pharmacy departments. This transition has resulted in substantial increases in pharmacy-related expenditure. For example, hepatitis C pharmacy spend grew nearly 200 percent in 2011 due to the U.S. Food and Drug Administration (FDA) approval of two new oral therapies.¹

Although the anticipated increase in pharmacy-related spend is daunting, resource utilization under the medical benefit cannot be ignored. Several specialty disease states, such as cancer, respiratory illnesses, and inflammatory conditions, have demonstrated year-over-year increases in their associated medical costs.¹ One contributing factor leading to the increased medical costs is the limited use of cost-effective administration locations (i.e., patient homes or physician

Total PMPY Specialty Drug Spend, 2006 vs. 2010¹



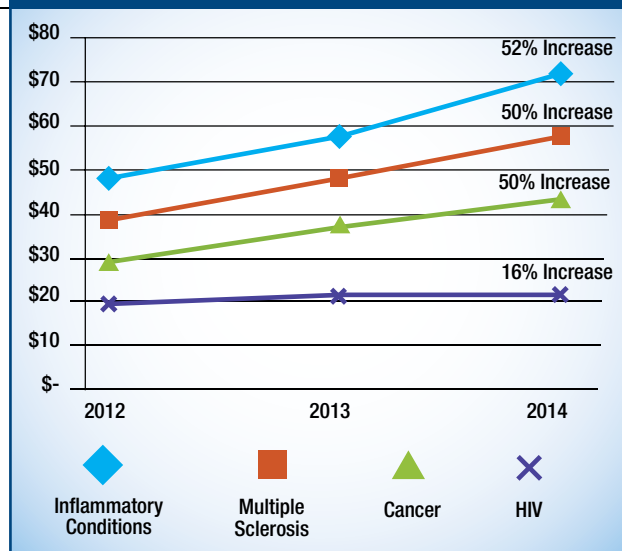
offices). The utilization of preferred administration sites has been gradually decreasing over time, which has a negative impact on the overall medical costs associated with infused specialty products and further demonstrates the need for a more structured management strategy.¹

Consistency of payment is another barrier that complicates specialty medication management. The reimbursement for some drugs is split between the medical and pharmacy departments, creating challenges when analyzing utilization data and developing management strategies. To help alleviate some of the ambiguity associated with their current technological limitations, many health plans are beginning to invest in information technology platforms that can integrate both medical and pharmacy data. These platforms can be used to analyze the total cost of care for specific disease states and assist in the development of policy controls to improve appropriate utilization and cost-effective care.

Introduction of Biosimilars

The federal government has taken notice of the increasing financial burden associated with specialty pharmaceuticals. A potential cost reduction strategy was incorporated into the Patient Protection and Affordable Care Act (PPACA). The PPACA has given the FDA authority to outline the approval process for biosimilar products. Once the criteria for biosimilar approval is complete, manufacturers will have a greater understanding of the research and application requirements needed to market a biosimilar. However, the economic impact that a biosimilar approval pathway will have on the U.S. healthcare system remains to be seen. Although these products will be considered “generic versions” of biologic products, the cost of these agents is only expected to be reduced by 20 to 30 percent.¹ These medications are expensive to develop and manufacture, so it is unlikely that more than two or three biosimilars will be approved for each branded biologic, further limiting the potential for competitive price reductions.

Estimated PMPY Cost for the Top Four Specialty Disease States, 2012 to 2014¹



Additionally, the perceived cost reductions of these “generic” products may enhance utilization of these expensive agents and further drive prescribing habits toward specialty drugs.¹ The major cost-saving potential of biosimilars lies in the ability of health plans to implement formulary controls and utilization management strategies to drive market share of preferred products and reduce unnecessary expenditures.

Proper management of specialty disease states is essential to contain the accelerating costs of these expensive medications. Ensuring that prescribers follow guidelines that are therapeutically beneficial, accredited, and cost-effective is ideal. Integration of clinical pathways assists in standardizing the care process with high-quality and evidence-based recommendations. Clinical pathways have been proven to enhance patient outcomes in addition to providing significant financial benefits.³ The multidisciplinary and structured approach helps integrate validated methods of measuring disease state activity with informed therapeutic management. Additionally, novel programs must work toward combining both pharmacy spend and medical spend. The current siloed approach to managing health plan pharmacy costs and turning a blind eye toward medical expenses will no longer be sustainable. Without the ability to integrate and manage both pharmacy and medical benefits efficiently, costs will continue to rise and care coordination will suffer.

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ACCOUNTABLE CARE ORGANIZATIONS

Inside a Pioneer ACO: Using Data to Deliver Quality

*Tara Canty, OSF HealthCare Chief Operating Officer of Accountable Care;
and Carl V. Asche, PhD, Director of the Center for Outcomes Research at the
University of Illinois College of Medicine at Peoria*

One of the most closely watched components of the Patient Protection and Affordable Care Act (PPACA) and other healthcare reform efforts is the development of Accountable Care Organizations (ACOs). These integrated delivery systems are designed to improve outcomes and control costs through better care coordination, use of patient-level data, and adherence to guideline-recommended care. In return, ACOs are reimbursed differently from the traditional fee-for-service basis, often sharing in any savings the new delivery systems generate. In some instances, ACOs are capitated for the populations they serve.

But how do ACOs differ from the capitation model of the 1980s and 1990s? Under that model, providers received a risk-adjusted per-member per-month (PMPM) payment to supply all primary care services for a given population. If they could provide the services for less than the amount received, they kept the difference. But they also bore most of the risk.

The reality is that the ACO model bears almost no similarity to the capitation model. Yes, the goal of both is to manage care more efficiently to reduce costs. But capitation garnered much criticism because of its focus on cost and utilization, rather than on quality and outcomes, with few, if any, capitation plans incorporating outcomes into their reimbursement formulas. The HMOs that administered capitation were often quite removed from members and providers, even operating in an adversarial role. They also generally capitated primary care practices only; specialty, outpatient, and hospital care was still reimbursed on a fee-for-service basis. This negated any possibility of truly impacting the quality and cost of care on a population basis.

ACOs, however, particularly as envisioned by the Centers for Medicare & Medicaid Services (CMS), focus on quality and improved health outcomes at a population level. The CMS Pioneer ACOs, for instance, must achieve a 90 percent score in 33 quality outcome measures in order to receive complete bonuses. Doing this requires that all ACO providers, from the primary care doctor to the hospital, work together to improve quality across the spectrum of patient care. Only if they meet these quality initiatives are they eligible to share in any savings based on historic spending levels.

To date, these savings occur as a bonus on top of traditional fee-for-service payments, but some commercial insurers are layering them atop a payment system that more resembles capitation, while others also require that providers share risk as well as savings. The 32 Pioneer ACOs began under either a shared benefit or shared risk model, transitioning to a partial capitation model in their third year.

We submit that there is another major difference between the capitation of the 1980s and 1990s, and the ACO model of today: technology. Thirty years ago, most patient records were still on paper. Assessing outcomes required waiting six months or more for claims data. Without real-time data, it is impossible to identify quality gaps in the system, assess the excess cost of those gaps, and develop interventions to reduce them.

Finally, the entire field of evidence-based medicine was just entering its infancy in the late 20th century. Even if we did have a way to monitor outcomes, we weren't really sure what those outcomes should be. Had the ACO concept been floated back then, it would have quickly been discarded as untenable.

Fast-forward to today, when 154 CMS-designed ACOs are providing care to 2.4 million Medicare beneficiaries, and dozens more are operating on the commercial side. Our focus is on utilizing the ACO model to ensure success for the OSF Healthcare System and our patients. We are just beginning the process, but by sharing what we know so far, we hope to provide a clearer path to the growing number of healthcare systems embarking upon ACOs.

Planning for a Paradigm Shift

OSF Healthcare System, owned and operated by the Sisters of the Third Order of St. Francis, serves more than 2.5 million people in Illinois and Michigan. We are a fully integrated healthcare system with eight hospitals and medical centers, one long-term care facility, and a physician network consisting of more than 600 primary care, specialist, and advanced practice providers.

By the time we submitted our Pioneer ACO application, we were already several years into planning for the coming paradigm shift from a traditional service-based payment system to today's value-based payment system. Among the first steps was re-engineering our 52 primary care practices into patient-centered medical homes

(PCMH). By the end of 2012, all will have Level 1 National Committee for Quality Assurance certification, and many will have Level 3 certification.

This is critical. Even the Agency for Healthcare Research and Quality (AHRQ) notes that PCMHs and ACOs are inextricably linked. The PCMH directly coordinates services for patients, and the ACO provides infrastructure and incentives to facilitate collaboration.¹ As Commonwealth Fund President Karen Davis, PhD, wrote:

“The patient-centered medical home is the foundation for everything that calls itself an ACO.”²

We also began modifying our reimbursement agreements with payors, even implementing a shared-risk contract with one major payor. We knew this was important because there is virtually no managed care penetration in the Peoria, Ill., market. Thus, there had been little oversight of care or care coordination. Developing this managed care environment required us, as providers, to begin approaching how we delivered that care differently, and that required different reimbursement models.

EPIC Gap Analysis

In 2011, we used data from our EPIC electronic health record system to conduct a detailed gap analysis. EPIC covers all episodes of care on the inpatient and outpatient sides, with full interaction in all care settings. We have embraced the system fully and are already meeting meaningful use criteria. With this data, we could ask the questions: Where are patients today? Where are the gaps in their care? Where are resources being wasted? Where can we find efficiencies in the system?

We firmly believe that without such a system—particularly one tied to the individual patient—you cannot have a successful ACO. Simply buying and using the system isn't enough, however. You and your providers must be fully engaged with it, able to run regular reports to identify trends, assess adherence, and measure outcomes. Our gap analysis showed us that we had to improve our management of high-risk, high-cost patients. Thus, we embedded a nurse

The Key to ACO Success

Because so much of the ACO model is based on quality outcomes, tracking and assessing those outcomes in real time to enable midcourse corrections, if necessary, is a critical component. We believe that plans that do not integrate this component into their overall models will not be successful.

care manager in every PCMH and provide care coordination to support that function. This is important because we found that social issues (income, education, transportation, etc.) are often tied to high utilization.

Under a fee-for-service plan, there is no reimbursement for addressing these “non-medical” issues. But under a shared-savings system, we have an incentive to do whatever we need to do to reduce utilization and improve outcomes. Now, instead of discarding an idea because of payment concerns, we ask ourselves: “What would we do if we take reimbursement out of the equation?” And then we do it. Often, prescription and meal delivery is what’s needed to keep patients out of the emergency room. Dedicated care managers are able to ascertain patient needs and find a resource to provide them.

Another major gap we identified is transitions of care. This is not just our gap, but a systemic gap throughout the United States. With changing payment policies on readmissions, it is finally getting the attention it deserves. Nationally, studies find that about a third of patients have at least one medication discrepancy upon discharge, nearly a fifth of Medicare beneficiaries are rehospitalized within 30 days (34 percent within 90 days), and half of those rehospitalized had never seen a physician after discharge.^{3,4} There is also evidence that about 13.3 percent of all readmissions at 30 days are potentially preventable.⁵

To address similar gaps in care, we are evaluating and will implement an inpatient risk assessment tool to identify patients at high risk of readmission. We have improved our procedure for medication management at discharge and our communication with outpatient providers who will follow the patient. A goal, of course, is to reduce our readmission rate, which is one of the 33 quality indicators.

Having a patient successfully transition home is the best outcome.

Another gap we identified is that our lengths-of-stay in skilled nursing facilities (SNFs) were four to five times the national average. To address this issue, we implemented a new process to transition patients to SNFs and hired a dedicated SNF practice composed of a physician, nurse practitioners, and care managers. Their only job is to manage patients in SNFs, going into the facilities to provide oversight and hands-on care, if needed.

We have since integrated the three years of patient data CMS provided to all Pioneer ACOs, followed by monthly reports on our members, with the EPIC data. It shows us where the problems are, what benchmarks to consider, and where there are opportunities for improvement. It enables us to stratify our patients by risk and identify those who need intensive care management. Although Medicare members could opt out from sharing this data, less than 1 percent of our ACO members did so.

Most of what we’re doing we view as “Level 1” of the ACO implementation. The goal is to drill further down into the data to identify goals for Level 2 implementation. This is where the Center for Outcomes Research comes in. What operational metrics should we be viewing in real time to monitor what we’re doing and where the care gaps are?

The Center for Outcomes Research

The Center for Outcomes Research is one of only a handful in the country directly supporting an ACO. The goal is to work closely with OSF to continue to identify gaps in quality and/or cost control, and to identify opportunities to close those gaps.

The first step is to continue OSF's data analysis. For instance, the Center will soon begin a project in the realm of appointment no-shows. Appointment cancellations and no-shows are expensive; one study in the community hospital setting found an average no-show rate of 62 appointments a day, at an estimated annual cost of \$3 million.⁶ Another analysis of a residency teaching clinic found that one in four visits was a no-show, and one in three patients was late, significantly affecting patient flow through the clinic.⁷ A study of no-shows and cancellations at a large family practice center found that the 31 percent no-show/cancellation rate could lead to a total annual revenue shortfall of 3 to 14 percent.⁸

Not only can no-shows affect a practice's bottom line, but they also result in delayed screenings and tests. This may delay disease detection, leading to higher acuity conditions and higher costs. It also affects continuity of care and can lead to increased use of higher-cost settings, such as emergency departments and urgent care centers.^{9,10}

The Center will use OSF's data from the EPIC system to assess the rate of no-shows and identify factors such as type of clinic, group versus individual practice, age, gender, and day of the week or year that affects no-shows. It will then determine the average cost per encounter in each clinic and the marginal cost of no-shows. By highlighting the most common reasons for no-shows, OSF can then identify interventions to reduce the rate and, ideally, demonstrate improved clinical outcomes and reduced costs.

The Center also plans to model the clinical and economic determinants of outcomes in patients with heart failure, a common and high-cost condition among Medicare beneficiaries.¹¹ Heart failure patients also have high rates of 30-day readmissions.¹² This study will use combined available data to describe the distribution of heart failure readmissions by age, sex, and other characteristics, as well as the frequency by clinic, seasonal variations, and readmissions by ZIP code. The Center will provide similar data on readmissions for patients with acute myocardial infarction and pneumonia. Another question to explore examines the reduction of lengths-of-stay throughout the system. For instance, are there less-expensive alternatives to inpatient hospitalization, such as SNFs?

Finally, the Center will also provide OSF with evidence to help develop clinical pathways and management plans. To that end, it hopes to organize a national group of Pioneer ACO outcomes experts to design and refine best practices and be consistent in their use. The result to all this is demonstrating improved outcomes at reduced costs.

Because so much of the ACO model is based on quality outcomes, tracking and assessing those outcomes in real time to enable midcourse corrections, if necessary, is a critical component. We believe that plans that do not integrate this component into their overall models will not be successful.

Editorial assistance was provided by Debra Gordon, MS

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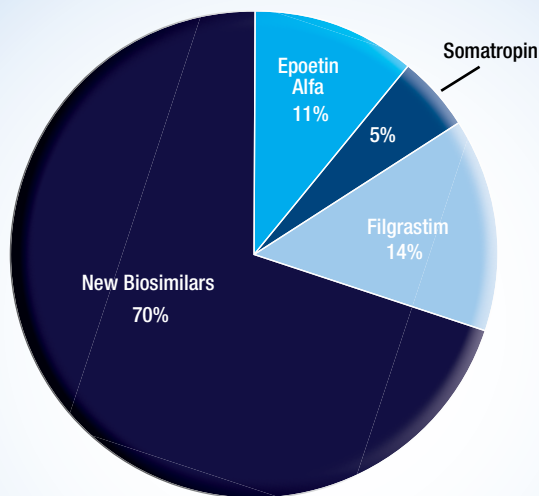
The Clinical and Financial Impact of Biosimilars

Mark McCamish, MD, PhD, Head of Global Biopharmaceutical Development, Sandoz International; and Nicholas Leazer

As the global population continues to grow and age, biologic drugs are increasingly being recognized as the only medications capable of effectively treating many complex diseases, including cancer and autoimmune disorders. Their unique ability to bind to specific targets within the body contributes significantly to improved survival rates, enhanced longevity, and better quality of life. Unfortunately, access to such products may be limited, due to their high cost. A biosimilar is a high-quality “duplicate” of an already-approved biologic drug that has lost patent protection. Although some variability exists in the manufacturing processes, biosimilars are designed to be comparable in terms of quality, safety, and efficacy, but they are expected to be less costly, thus improving patient access.

The global market for biosimilars is expanding. Global sales of biosimilars are projected to grow to \$2.6 billion by 2015, up from \$378 million in 2011.¹

Projected Global Biosimilar Sales (2011-2015)



Several top-selling biologics, including Herceptin, Humalog, Remicade, and Aranesp, are set to lose their patents within the next few years. Estimates place the patent loss for biologics between now and 2016 at \$51 billion. Biosimilars may be off to a slow start, but it is likely that an influx of products will be observed as more and more patents begin to expire.

Source: IMS Health. IMS MIDAS biosimilars data. 2010-2011.



Due to the rising cost of healthcare and the increasing prevalence of biologic medications, biosimilars can have a great impact on patients, prescribing physicians, and managed care organizations. With cancer, diabetes, and rheumatoid arthritis accounting for almost half of the biologic products on the market, there is no shortage of patients who could benefit from lower-cost medications.



In the United States, the recent healthcare reform legislation is paving the way to enhanced market access for biosimilars. It is estimated that within the first year of competition, biosimilars will account for 10 percent of the national market share for biologic products, and that by the fourth year of competition, biosimilars will account for more than 35 percent.² With the

total global market of all biologic medications, both brand and biosimilar, estimated to be \$138 billion annually,¹ there is a huge economic potential for biosimilars, especially in the United States.

Estimates have placed the overall cost-savings associated with the biosimilar market at slightly more than \$25 billion between now and 2018 in the United States, and \$33 billion in Europe through 2020.³ This includes the estimated \$6.6 billion in savings seen by the federal government, \$4.7 billion from Medicare alone.² To allow for competitive pricing, the cost of developing biosimilars, while high, must still be lower than that of branded biologics. Although it costs approximately \$1.2 billion to develop a brand name biologic, including costs for many failures along the way, it is estimated that a biosimilar will cost about \$150 million to \$250 million to bring to market.¹ A large proportion of biologic products currently on the U.S. market (45 percent) are used to treat the common conditions of cancer, diabetes, and rheumatoid arthritis.¹ Although many of the biologics indicated for these disease states will retain patent protection for several years, these three disease states represent the greatest potential for profit in the biosimilar market.

Impact of the PPACA and FDA Guidance

The Patient Protection and Affordable Care Act (PPACA), signed into law in March of 2010, authorizes the U.S. Food and Drug Administration (FDA) to create a pathway for

the licensure and approval of biosimilar products. These products are expected to have the same safety and efficacy profiles compared to the original biologics.⁴ In addition, the legislation allows the FDA to approve an interchangeable biosimilar that can be substituted with the originator biologic by the pharmacists. This second category of interchangeable biosimilars is not currently available in other regulatory regions, such as Europe, and will likely require additional data to be submitted for approval. Pharmaceutical manufacturers can file for biosimilarity and interchangeability at the same time, but the final categorization will be determined by the FDA.⁵ According to the PPACA, a “biosimilar product” is a biologic medication that has “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”⁴ If a patient is administered a biosimilar, the expectation will be that the patient’s response to therapy will not be clinically different than if he or she were prescribed the corresponding branded product.

The PPACA also defines the exclusivity period of original biologic products. After the approval of this legislation, branded biologic drugs, or “reference products,” will now be granted 12 years of exclusivity from the original date of FDA approval. Additionally, if the Biologics License Application (BLA) contains results from pediatric studies, the FDA will grant an additional six months of patent exclusivity. In addition, for the first biosimilar product to be granted interchangeability to the reference product, the PPACA allows for a 12- to 42-month exclusivity period; this time frame is dependent on pending or current litigation against the sponsor of the biosimilar product.⁴

On February 9, 2012, the FDA released preliminary guidelines for the biosimilar approval process. These draft guidelines contain initial thoughts regarding what information should be provided by manufacturers wishing to apply for a biosimilar approval. In order to allow for abbreviated clinical testing, the FDA recommends

extensive structure and function testing of the biosimilar product compared to the reference product, along with data demonstrating high-similarity between products.⁵ The approach outlined in these guidelines is similar to the processes in place in Canada, Japan, and Europe, wherein most biosimilars must undergo at least one safety and efficacy clinical trial in patients.¹

The FDA states that, should a biosimilar product be “highly-similar” to the reference product in terms of structure and function, and in human and animal pharmacokinetic/

pharmacodynamic studies, there would likely be a need only for focused or abbreviated clinical trials. However, if there are large differences in the structure of the biosimilar and the reference product, the FDA would likely require much more evidence supporting the lack of clinically significant differences between the products, including more extensive clinical trials. The FDA also recommends that the sponsor of the biosimilar product consult with them at multiple points during the initial testing and clinical trials in order to review the information and provide

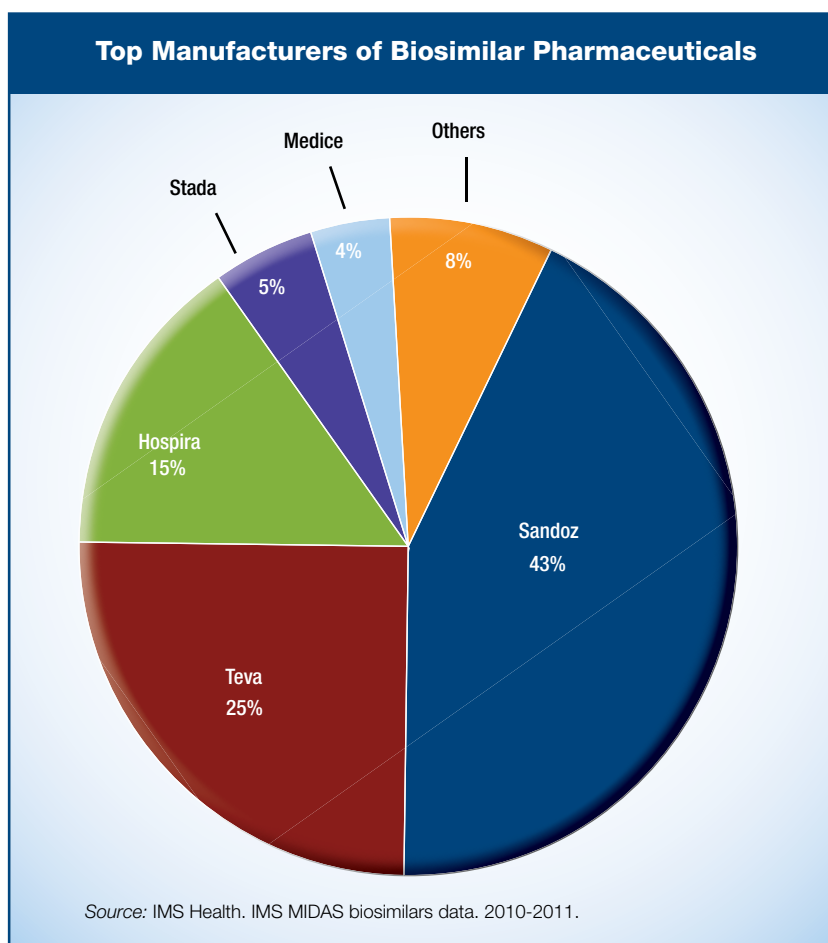
feedback in regard to the direction of further studies.⁵

Although the FDA’s draft guidelines mention the interchangeability of a biosimilar product, the FDA has not yet developed internal policies regarding the regulatory approach to approval of an interchangeable biosimilar. For a biosimilar to be deemed “interchangeable,” the sponsor must prove that the risk to the patient of switching to their product in the middle of therapy is no greater than the risk of continuing the branded product. Therefore, most sponsors pursuing an interchangeable approval are planning to conduct switching studies to provide such data to the FDA. Only biosimilars that have been approved as “interchangeable” will be able to be automatically substituted from the branded originator drug. Manufacturers that do not gain the approval for interchangeability will have to promote their drugs to doctors and hospitals with materials educating them on the merits of their drugs, much as they do now with branded competitors.

Merck, Pfizer, and Novartis are all preparing to develop biosimilars for branded agents currently on the market. Amgen has partnered with generic manufacturer Watson to create a biosimilar for an unspecified cancer medication. Teva, Sandoz, Hospira, and Stada already have biosimilar agents approved in Europe and may consider applying for approval in the United States.¹

Economic Impact of Biosimilars

Due to the rising cost of healthcare and the increasing prevalence of



biologic medications, biosimilars can have a great impact on patients, prescribing physicians, and managed care organizations. With cancer, diabetes, and rheumatoid arthritis accounting for almost half of the biologic products on the market, there is no shortage of patients who could benefit from lower-cost medications. While the anticipated cost reduction of biosimilar agents is 25 to 30 percent, discounts of up to 50 percent have been experienced in Europe; therefore, the increased market competition may produce a substantial opportunity for cost-containment strategies. For managed care organizations, contracting opportunities and formulary management will be important in reducing the overall cost to health plans as the number of biosimilars on the market increases. Additionally, the development and implementation of clinical pathways and prescriber education will be important in minimizing the overall costs of care. These pathways can offer a stepwise approach to therapy, identify preferred health plan agents, ensure appropriate evaluation and monitoring, and recommend the use of cost-effective administration sites, if necessary.

While biosimilars will provide less expensive alternatives to the current branded biologics, structured management will be extremely important



in promoting appropriate utilization of these medications. A potential concern within managed care is the increased use of biologic medications as more products become available. Physicians may be more likely to initiate patients on biologic therapy sooner in the course of therapy when they would have previously continued with a more traditional oral medication. However, earlier use of biologics and pathways of care may result in

the prevention of disability associated with diseases such as rheumatoid arthritis. Providing these physicians with a more structured management strategy that is supported by best practice guidelines can help to optimize healthcare through improved access, while also minimizing the potential for inappropriate utilization and helping contain the inevitable healthcare expenditure associated with these agents.

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PIPELINE TRENDS

NEW DRUG APPROVALS

Hypertriglyceridemia

Vascepa® (icosapent ethyl)
Approved: July 26, 2012
Formulation: capsule
Manufacturer: Amarin Corp.

Indication: Vascepa® (icosapent ethyl) is an ethyl ester of eicosapentaenoic acid (EPA) indicated as adjunct therapy to diet to reduce triglycerides in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Inflammation/Immunosuppression

Rayos® (prednisone)
Approved: July 26, 2012
Formulation: delayed-release tablet
Manufacturer: Horizon Pharma, Inc.

Indication: Rayos® (prednisone) is a delayed-release corticosteroid indicated in the treatment of various diseases, including rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma, and chronic obstructive pulmonary disease (COPD).

OBESITY

Belviq® (lorcaserin)
Approved: June 27, 2012
Formulation: tablet
Manufacturer: Arena Pharmaceuticals, Inc.

Indication: Belviq® (lorcaserin) is a serotonin 2C receptor agonist indicated as adjunct therapy in weight-loss management for adults who are obese or overweight with at least one weight-related comorbidity.

Qsymia™ (phentermine and topiramate extended-release)
Approved: July 17, 2012
Formulation: capsule
Manufacturer: Vivus, Inc.

Indication: Qsymia™ (phentermine and topiramate extended-release) is a combination product indicated as adjunct therapy to weight-loss management in adults who are obese or overweight with at least one weight-related comorbidity.

OVERACTIVE BLADDER

Myrbetriq™ (mirabegron)
Approved: June 28, 2012
Formulation: extended-release tablet
Manufacturer: Astellas Pharma US

Indication: Myrbetriq™ (mirabegron) is a β -3 adrenergic agonist indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

PULMONARY

Tudorza™ Pressair™ (aclidinium bromide)
Approved: July 23, 2012
Formulation: powder for inhalation
Manufacturer: Forest Laboratories, Inc., and Almirall, S.A.

Indication: Tudorza™ Pressair™ (aclidinium bromide) is an inhaled anticholinergic approved for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

NEW SPECIALTY PRODUCT APPROVALS

BREAST CANCER

Perjeta™ (pertuzumab)
AWP: \$4,809.79/pkg
WAC: \$4,075.66/pkg
Approved: June 8, 2012
Formulation: injection
Manufacturer: Genentech

Indication: Perjeta™ (pertuzumab) is an intravenous infusion approved for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. It is used in combination with trastuzumab and docetaxel; combination therapy is expected to exceed \$100,000 per patient per year.

MULTIPLE MYELOMA

Kyprolis™ (carfilzomib)
Approved: July 20, 2012
Formulation: injection
Manufacturer: Onyx Pharmaceuticals, Inc.

Indication: Kyprolis™ (carfilzomib) is a proteasome inhibitor indicated in the treatment of patients with multiple myeloma who have received two previous therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Treatment is expected to average \$40,000 per patient.

Disclosures: The information contained in Pipeline Trends is current as of August 2012. 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.

NEW FDA-APPROVED INDICATIONS

Drug Name	Approved	New Indication
Afinitor® (everolimus)	July 20, 2012	HER2(+) breast cancer in postmenopausal women
Truvada® (emtricitabine/tenofovir)	July 16, 2012	Pre-exposure prophylaxis for HIV infection
Gammagard Liquid® (immune globulin infusion [human])	June 25, 2012	Multi-focal motor neuropathy
Afinitor® (everolimus)	April 26, 2012	Non-cancerous kidney tumors (angiomyolipoma)
Votrient® (pazopanib)	April 26, 2012	Advanced renal cell carcinoma

NEW FIRST-TIME GENERIC DRUG APPROVALS

Drug Name	Launch Date
Abacavir sulfate oral tablet (Ziagen®) (6-25mg, 6-50mg, 12-25mg, 12-50mg capsules)	June 18, 2012
Clindamycin phosphate/benzoyl peroxide 1.2%-5% topical gel (Duac®)	June 26, 2012
Desloratadine oral tablet (Clarinet®)	July 1, 2012
Montelukast sodium oral tablet (Singulair®)	Approved: August 2012
Nevirapine oral suspension (Viramune®)	May 21, 2012
Nevirapine oral tablet (Viramune®)	May 21, 2012
Voriconazole intravenous solution (Vfend®)	May 30, 2012

PROJECTED FIRST-TIME GENERIC ENTRY

Drug Name	Launch Date
Dexamethylphenidate HCl extended-release (Focalin® XR)	October 2012
Lidocaine topical patch (Lidoderm®)	November 2012
Pioglitazone/metformin (Actoplus Met®)	December 2012
Candesartan (Atacand®)	December 2012
Candesartan-hydrochlorothiazide (Atacand® HCT)	December 2012
Rizatriptan (Maxalt®) tablet, orally disintegrating tablet	December 2012
Betamethasone valerate (Luxiq®)	January 2013
Oxymorphone HCl (Opana® ER)	January 2013
Finasteride (Propecia®)	January 2013
Fluvoxamine controlled-release (Luvox® CR)	February 2013
Zoledronic acid (Reclast®)	March 2013
Zoledronic acid (Zometa®)	March 2013
Valganciclovir HCl (Valcyte®)	March 2013

COMING SOON ...

SPECIALTY

Product Name	Manufacturer	Route of Administration	Filing Status	Proposed Indication
Metreleptin	Amylin	SQ injection	PDUFA Oct. 3, 2012	Diabetes and hypertriglyceridemia in patients with lipodystrophy
Ocriplasmin	ThromboGenics	Intraocular injection	PDUFA Oct. 17, 2012	Symptomatic vitreomacular adhesion
Factor IX	Inspiration	Intravenous injection	BLA submitted April 2012	Treatment and prevention of bleeding episodes in patients with hemophilia B
Treprostinil (Remodulin®)	United Therapeutics	Oral	PDUFA Oct. 27, 2012	Treatment of pulmonary arterial hypertension
Cabozantinib	Exelixis	Oral	PDUFA Nov. 29, 2012	Medullary thyroid cancer
Bosutinib	Pfizer	Oral	PDUFA Oct. 2012	Chronic myelogenous leukemia

Androgen Receptor Inhibition in Advanced Prostate Cancer

Prostate cancer is one of the most common types of cancer and is the second-leading cause of cancer-related death in American men. In 2012, it is estimated that there will be more than 240,000 new cases of prostate cancer.¹ Prostate cancer is associated with an annual expenditure of more than \$9.8 billion in the United States, according to some estimates.² As the U.S. population is progressively aging, this problem is only projected to intensify and represents a serious public health concern.

Early diagnosis is essential to improve outcomes for patients with prostate cancer and reduce the associated healthcare costs. Unfortunately, in many patients, prostate cancer initially goes undiagnosed, as most of the early symptoms mirror those of benign prostatic hyperplasia. As a result, a large number of patients have already progressed to advanced stages upon diagnosis. According to the American College of Surgeons, 33 percent of patients have late-stage prostate cancer when diagnosed.³

Factors Leading to Tumor Growth

Prostate cancer growth is dependent on signaling by the androgen receptor (AR).^{4,5,6} The key components of the androgen signaling cascade, and subsequently tumor proliferation, include androgen production, androgen binding, nuclear translocation, and DNA binding and transcription of tumor growth genes. For more than six decades, depleting androgens or decreasing androgen action have been the mainstay of prostate cancer treatment.

Testosterone, which is made predominantly in the testes, is the primary androgen in men and is the major source of prostate cancer growth.⁴ The AR, an intracellular receptor found on prostate cancer cells, can be considered the vehicle that drives tumor growth, and androgens, such as testosterone and dihydrotestosterone (DHT), are the gasoline that powers the process. The AR is activated when androgens bind to the receptor and upon activation, the AR complex translocates into the nucleus of the prostate cell.⁴ Once the AR complex reaches the nucleus, it binds to DNA and initiates transcription of androgen receptor-dependent genes required for cancer cell growth.^{4,7}

Although direct AR activation by androgens is the primary mechanism for tumor growth, in many patients, AR signaling can still persist, despite depletion of androgens to castration-like levels. This signaling is facilitated by additional activation mechanisms, including receptor overexpression, testosterone-independent receptor activation, and receptor activation by non-androgens. When these activation mechanisms occur, the condition is known as castration-resistant prostate cancer (CRPC).

■ **AR overexpression:** A common molecular alteration in progressive CRPC that results in increased tumor cell sensitivity to very low residual levels of androgens. Overexpression of AR can cause the growth of tumor cells even after aggressive androgen deprivation therapy.⁸

■ **Testosterone-independent receptor activation:** Variants of the AR can



maintain signaling activity and drive tumor progression even in the absence of testosterone or DHT. This is usually facilitated by other intrinsic growth factors.⁷

■ Receptor activation by non-androgens: Mutations in the AR can allow for activation by non-androgens and cause AR promiscuity.^{9,10} These mutations allow for the activation of the AR signaling pathway by progesterone, estrogen, hydrocortisone, and prednisone.^{5,7,9,11,12}

If the tumor growth is enhanced by one or more of these pathways, the traditional mainstay of andro-

gen deletion will not be enough to mitigate tumor cell proliferation. Currently, researchers are evaluating several new pharmaceutical products with novel mechanisms of action designed to inhibit the activation, and subsequent cell growth, through each of these castration-resistant pathways.

Introduction to a Novel Mechanism

As the AR cascade can be activated via several mechanisms, the ultimate goal of prostate cancer therapy should be to inhibit cellular growth from DNA binding and transcription, the

final stage in the pathway leading to tumor growth, cancer cell differentiation, and survival. Inhibition of this final step of the cascade is now the focus of research and development in new prostate cancer therapies.

One chemical entity that is currently under review by the U.S. Food and Drug Administration (FDA) is uniquely designed to target several steps along the AR cascade, including DNA binding and transcription. In July 2012, it was announced that enzalutamide (formerly MDV3100), a novel androgen receptor signaling inhibitor (ARSI), will receive a priority review by the FDA. Enzalutamide is an oral, once-daily experimental therapy attempting to gain FDA approval for the treatment of CRPC in patients following chemotherapy. In preclinical models, enzalutamide has been shown to inhibit multiple steps in the AR signaling pathway, even after androgen deprivation (Figure 1). Through the androgen antagonist activity, enzalutamide has been demonstrated to:

- Inhibit binding of androgens to AR
- Inhibit nuclear translocation of the AR-complex
- Inhibit the association of the AR-complex with DNA

As a result of inhibiting the AR signaling cascade, specifically the activated AR-complex with DNA, enzalutamide blocks the transcription of genes required for cancer cell growth and facilitates tumor cell death. The clinical benefits of this agent in patients with CRPC have been extensively studied in premarket trials, the most comprehensive being the AFFIRM Study.

AFFIRM Study Results

The survival benefits of enzalutamide were evaluated in a phase 3 clinical trial, known as the AFFIRM study. AFFIRM was a randomized, double-blind,

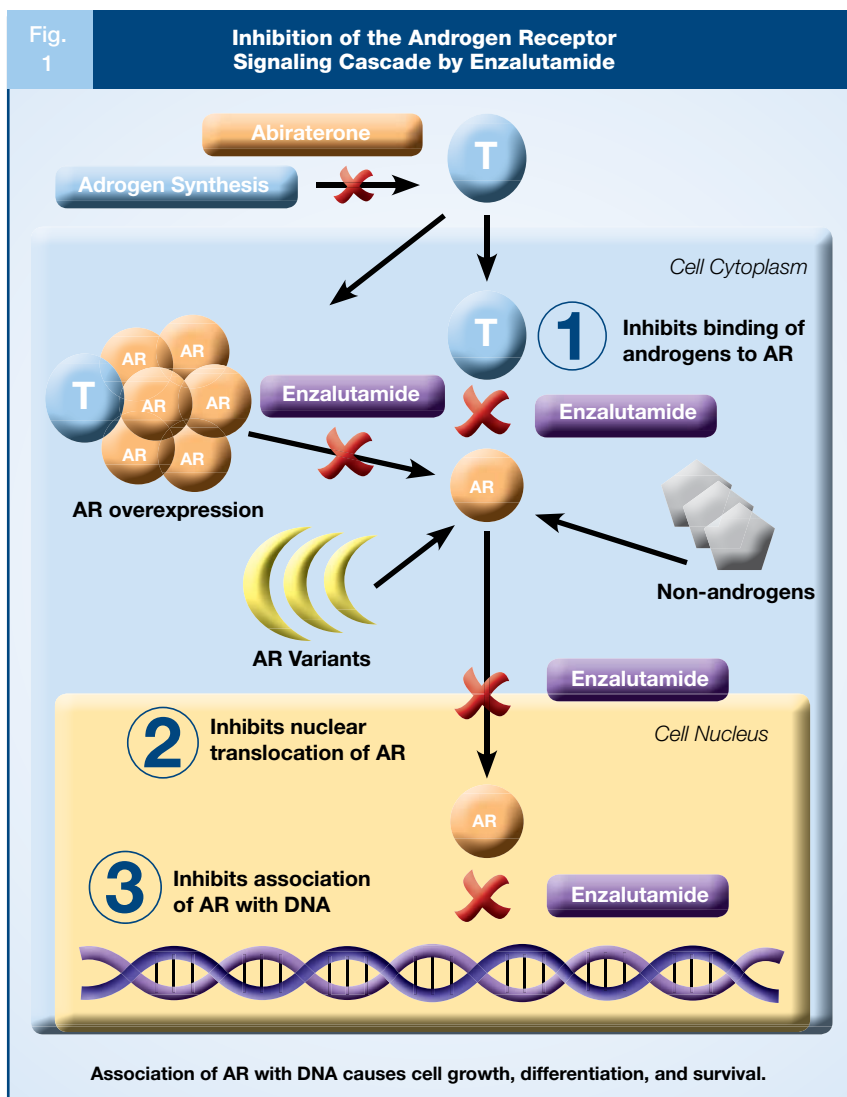


Table 1	Summary of Adverse Events: AFFIRM Study ¹³	
	All Reported Events	
	Enzalutamide n=800	Placebo n=399
Adverse events	98.1%	97.7%
Serious adverse events	33.5%	38.6%
Discontinuations due to adverse events	7.6%	9.8%
Adverse events leading to death	2.9%	3.5%

placebo-controlled, multinational study conducted at 156 centers in 15 countries. Enrollment began in September 2009 and patients were randomized (2:1) to either enzalutamide 160 mg once-daily or a matching placebo. The primary endpoint observed in this trial was overall survival. Patients received enzalutamide, the study drug, for a median duration of 8.3 months, while patients receiving placebo were only on it for a median duration of 3.0 months. For patients in the enzalutamide treatment arm, the median overall survival was 18.4 months compared to 13.6 months for patients taking the placebo. This 4.8-month survival benefit correlated to a 37 percent reduction in the risk of death for patients with advanced prostate cancer.¹³ Based on the statistically significant and clinically meaningful overall survival benefit, the data monitoring committee (DMC)

recommended that the AFFIRM study be halted and unblinded and that eligible patients in the placebo arm be offered treatment with enzalutamide. This study demonstrates the survival benefits that can be observed in patients with advanced CRPC if the right targeted therapy is used to reduce AR signaling.

The Future of CRPC Therapy

Prostate cancer cell proliferation, differentiation, and survival can be enhanced by several different mechanisms in the AR signaling pathway. For many patients, androgen depletion is not enough to reduce tumor cell growth. New therapies that target multiple activation mechanisms within the AR signaling cascade, such as enzalutamide, are essential to extend survival in patients with advanced CRPC. Although this therapy has only been proven in patients following

failure of docetaxel therapy, additional phase 3 trials are currently under way. The PREVAIL trial is a randomized, double-blind, placebo-controlled, multi-national study in patients with metastatic prostate cancer who are progressing despite treatment with androgen deprivation therapy. This trial is being conducted in patients who have not yet received chemotherapy with docetaxel. Depending on the results of PREVAIL, enzalutamide may have a substantial therapeutic advantage in the treatment of advanced CRPC and could potentially limit the amount of chemotherapy needed to treat these patients.

As the U.S. population is steadily aging, the health and economic concerns associated with prostate cancer will only progress with time. Novel therapeutic alternatives should be researched with the goal of extending survival, limiting the need for chemotherapy, mitigating tumor growth, and reducing unnecessary adverse reactions. Pharmaceutical products that are able to achieve these goals will enhance the quality of care offered to patients with advanced prostate cancer and ensure that maximum health and survival benefits are obtained.

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Victoza® (liraglutide [rDNA origin] injection)

Rx Only

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

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

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

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

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

pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues [see Adverse Reactions]. **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 [see Adverse Reactions]. 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 [see Adverse Reactions]. 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. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

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

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

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

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

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

Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
Adverse Event Term	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Decreased Appetite	9.3	1.1	
Anorexia	9.0	0.0	
Headache	8.2	4.6	
Constipation	5.1	1.1	
Fatigue	5.1	1.7	

Table 3: Treatment-Emergent Adverse Events in 26 Week Open-Label Trial versus Exenatide (Adverse events with frequency ≥5% and occurring more frequently with Victoza® compared to exenatide are listed)

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea N = 232
Preferred Term	(%)	(%)
Diarrhea	12.3	12.1
Dyspepsia	8.9	4.7
Constipation	5.1	2.6

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

duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 4). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 4: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

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

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

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdose, 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., 100 College Road West, Princeton, New Jersey 08540, 1-877-484-2869

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

Victoza® is a registered trademark of Novo Nordisk A/S. Victoza® is covered by US Patent Nos. 6,268,343; 6,458,924; and 7,235,627 and other patents pending. Victoza® Pen is covered by US Patent Nos. 6,004,297; 6,235,004; 6,582,404 and other patents pending.

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VICTOZA®
liraglutide (rDNA origin) injection

Help adult patients with type 2 diabetes gain greater access

Get to know Victoza® on a deeper level.

Powerful reductions in A1C from -0.8% to -1.5%*

A1C



Low rate of hypoglycemia



May reduce weight

—Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials



Flexible dosing any time of day, independent of meals



VictozaCare™ helps patients stay on track with ongoing support

—Patients enrolled in VictozaCare™ were more adherent to Victoza® than those not enrolled†

*Beta cells
glucose*



To see how Victoza® works for your patients, visit **VictozaPro.com/GLP1**.

VICTOZA®
liraglutide (rDNA origin) injection

Indications and usage

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

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

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

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

The concurrent use of Victoza® and insulin has not been studied.

Important safety information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum

calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

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

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

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.

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

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

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

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

Please see brief summary of Prescribing Information on adjacent page.

*Victoza® 1.2 mg and 1.8 mg when used alone or in combination with OADs.

†Crossix ScoreBoard™ Report, September 2011. Adherence measured by number of actual Victoza® prescriptions filled for existing Victoza® patients enrolled in VictozaCare™ versus a match-pair control group not enrolled in VictozaCare™ through first 8 months of enrollment.

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