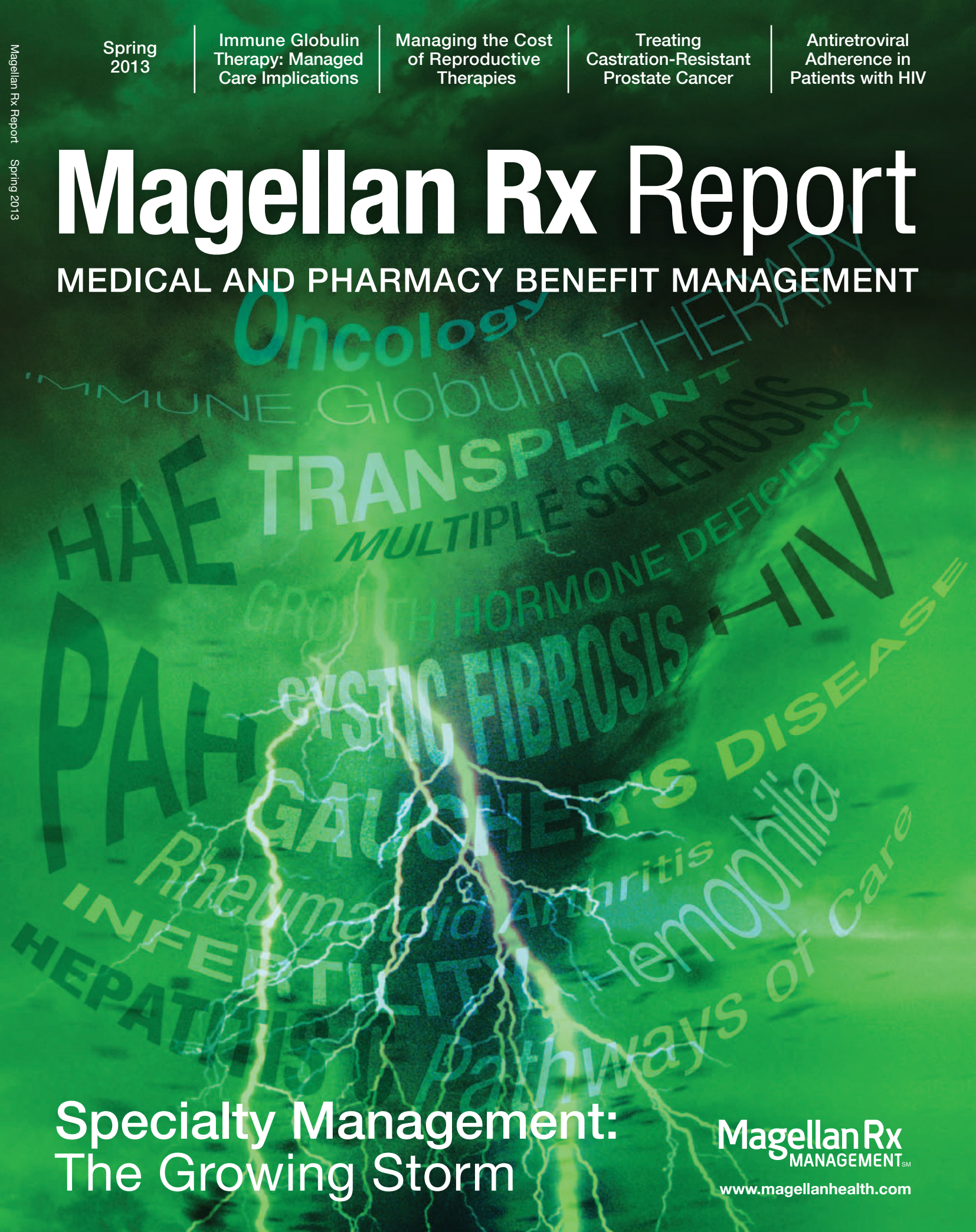
Spring 2013 | Immune Globulin Therapy: Managed Care Implications | Managing the Cost of Reproductive Therapies | Treating Castration-Resistant Prostate Cancer | Antiretroviral Adherence in Patients with HIV

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT



Specialty Management: The Growing Storm

Magellan Rx MANAGEMENT℠

www.magellanhealth.com

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

NOW APPROVED

FOR PATIENTS WITH mCRPC WHO HAVE PROGRESSED ON ADT

ADT = androgen-deprivation therapy.

IMPORTANT SAFETY INFORMATION

- **Contraindications**—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.
- **Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess**—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in study 1) or NYHA Class II to IV heart failure (in study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.
- **Adrenocortical Insufficiency (AI)**—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.
- **Hepatotoxicity**—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.
- **Increased ZYTIGA® Exposures With Food**—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

INTRODUCING

AN EXPANDED BODY OF EVIDENCE

More than 20,000 patients with mCRPC have received ZYTIGA® (post-chemotherapy with docetaxel) to date.†[1]

MECHANISM OF ACTION

ZYTIGA® is a CYP17 (17α-hydroxylase/C17, 20-lyase) inhibitor that inhibits androgen production at 3 sources: the testes, adrenal glands, and the prostate tumor tissue itself.

NEW EFFICACY DATA **—In a recent Phase 3 clinical trial in patients with mCRPC who had progressed on ADT and had not received chemotherapy.***

Efficacy was also demonstrated in a Phase 3 trial of patients who had received prior chemotherapy containing docetaxel.*

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

ZytigaOne™ is your single source for personalized access services for you and your patients: Visit www.zytigaone.com or call 1-855-998-4421.

ZytigaOne™ SUPPORT
The Janssen Biotech Support System

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

  The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.
- **Drug Interactions**—ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. *In vitro*, ZYTIGA® inhibits CYP2C8. There are no clinical data on its use with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

  Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution during treatment with ZYTIGA®.
- **Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

K08Z121176

***Study Designs:** *ZYTIGA®, in combination with prednisone, was evaluated in 2 Phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients with mCRPC. Study 1 enrolled patients who received prior chemotherapy containing docetaxel (N = 1,195), whereas Study 2 enrolled patients who had not received prior chemotherapy (N = 1,088). In both studies, patients were using a luteinizing hormone-releasing hormone agonist or were previously treated with orchiectomy. In the active treatment arms, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the control arms, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In Study 1, the primary efficacy endpoint was overall survival. In Study 2, the coprimary efficacy endpoints were overall survival and radiographic progression-free survival.*

† *Estimate based on sales and use data from May 2011 to November 2012.*

Reference: 1. Data on file. Janssen Biotech, Inc.

www.zytigahcp.com

Please see adjacent pages for brief summary of full Prescribing Information.

Janssen Biotech, Inc.

12/12 08Z12264A

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

Table 1: Adverse Reactions due to ZYTIGA in Study 1

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

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

[4]Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5]Includes all fractures with the exception of pathological fracture
[6]Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7]Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8]Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

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

Table 2: Laboratory Abnormalities of Interest in Study 1

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

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

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

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

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

ZYTIGA® (abiraterone acetate) Tablets

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

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

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

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

[1]Based on non-fasting blood draws

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

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

DRUG INTERACTIONS

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

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

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

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

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

OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.

ZYTIGA® (abiraterone acetate) Tablets

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

Manufactured by:
Patheon Inc.
Mississauga, Canada

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044

Revised: December 2012

2000005445

K08Z121174A

janssen

Letter from the President

Susan Petrovas

Dear Managed Care Colleagues,

Susan Petrovas, RPh, President

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

As you all know, the management of specialty pharmaceuticals has placed a substantial amount of clinical pressure and financial burden upon managed care organizations. The growth of the specialty pharmaceutical industry has created considerable challenges for health plans trying to improve the quality of care provided to patients utilizing these products, while also being aware of the economic implications. As many specialty products significantly influence both the pharmacy and medical budgets, structured and coordinated management approaches are needed to help manage the growing number of specialty pharmaceuticals entering the marketplace.

Managed care organizations across the country are implementing disease state management initiatives for specialty categories that have the greatest impact on healthcare resources. Categories such as inflammatory diseases, multiple sclerosis, hepatitis C, and oncology are being addressed through a variety of strategies designed to control costs and improve patient outcomes. However, there are several other specialty categories that remain inadequately managed. Conditions including hereditary angioedema, Gaucher's disease, intravenous immunoglobulin (IVIg) therapy, and pulmonary arterial hypertension all help drive the financial burden associated with specialty pharmaceuticals. These conditions present unique management challenges that many health plans do not have sufficient time, expertise, or resources to appropriately address.

CDMI now represents more than 57 million patients who receive insurance coverage from 40 health insurance plans across the country. We have committed a substantial amount of time and resources to developing specialty management solutions to improve the quality of care delivered by our payor customers. These solutions include formulary management and compliance, adherence and persistency programs, clinical pathways of care, quality performance improvement programs, site-of-care optimization, care coordination, and patient-centered care.

For additional information regarding these clinical offerings, or any of CDMI's services, please feel free to contact me at **SPetrovas@CDMIhealth.com.** As always, I value any feedback that you have on the issue. Thank you for reading!

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

CDMI REPORT

ISSN: 2159-5372

PUBLISHED BY:
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WELCOME

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For the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF) or other conditions

ULTRESA™ helps treat malabsorption* and stool symptoms of EPI[1-2]

Important Safety Information

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of ULTRESA 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 ULTRESA or retain in mouth
- Exercise caution when prescribing ULTRESA to patients with gout, renal impairment, or hyperuricemia
- There is theoretical risk of viral transmission with all pancreatic enzyme products, including ULTRESA
- 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
- The most common adverse reactions (≥7% of patients treated with ULTRESA) were headache, pharyngolaryngeal pain, and epistaxis
- Use of ULTRESA in pediatric patients is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight
- ULTRESA is not interchangeable with any other pancrelipase product

***Reduction in malabsorption is shown by improvement in coefficient of fat absorption (CFA), primary endpoint, and coefficient of nitrogen absorption (CNA), secondary endpoint.[1-2]**

References: 1. Konstan MW, Liou TG, Strausbaugh SD, et al. Efficacy and safety of a new formulation of pancrelipase (Ultrase MT20) in the treatment of malabsorption in exocrine pancreatic insufficiency in cystic fibrosis. *Gastroenterol Res Pract*. 2010. **2.** Data on file (UMT20CF05-01), Aptalis Pharma US, Inc., Bridgewater, NJ.

Please read brief summary of full US Prescribing Information on following pages.

Ultresa™ (pancrelipase) Delayed-Release Capsules

APTALIS™

ULTRESA (pancrelipase) delayed-release capsules, for oral use
Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR ULTRESA (pancrelipase) delayed-release capsules: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

ULTRESA™ (pancrelipase) is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

2 DOSAGE AND ADMINISTRATION

ULTRESA is not interchangeable with other pancrelipase products.

ULTRESA is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of ULTRESA should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet as described in the Limitations on Dosing below *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

2.1 Administration

Children and Adults

ULTRESA should be taken during meals or snacks, with sufficient fluid. ULTRESA capsules should be swallowed whole. ULTRESA capsules and capsule contents should not be crushed or chewed.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on a small amount of applesauce, yogurt and other acidic soft food with a pH of 4.5 or less at room temperature.

The ULTRESA-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth to avoid mucosal irritation.

Any unused portion of capsule contents should be discarded, and not used for subsequent dosing. The remaining exposed contents may lose potency and become less effective.

2.2 Dosage

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences. ULTRESA should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraphs. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Children Older than 12 Months and Younger than 4 Years and Weight 14 kg or Greater

Children older than 12 months and younger than 4 years, weighing under 14 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Weight 28 kg or Greater and Adults

Children 4 years and older, weighing under 28 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed ULTRESA dose for an individualized full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

Limitations on Dosing:

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. If symptoms and signs of steatorrhea persist, the dosage may be increased by a healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted.

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. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age *[see Warnings and Precautions (5.1)]*. Patients currently 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.

Use of ULTRESA in children is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Attempting to divide the capsule contents in small fractions to deliver small doses of lipase is not recommended.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 with use 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)]*.

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.

5.2 Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth. ULTRESA should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity *[see Dosage and Administration (2.1) and Patient Counseling Information (17.1) in the full prescribing information]* For patients who are unable to swallow intact capsules, the contents may be sprinkled on applesauce, yogurt and other acidic soft food with pH 4.5 or less. The ULTRESA-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

5.3 Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing ULTRESA to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

5.4 Potential for Viral Exposure from the Product Source

ULTRESA is sourced from pancreatic tissue from pigs used for food consumption. Although the risk that ULTRESA 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.

5.5 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 ULTRESA treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

6 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 (5.1, 5.3 and 5.5)]*.

6.1 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 clinical practice.

The short-term safety of ULTRESA was assessed in two clinical trials conducted in 40 patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). Study 1 was conducted in 31 patients, ages 8 years to 37 years; Study 2 was conducted in 9 patients, ages 7 years to 11 years.

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 31 patients, ages 8 to 37 years, with EPI due to CF. In this study, patients were randomized to receive ULTRESA at doses not to exceed 2,500 lipase units per kilogram per meal or matching placebo for 6 to 7 days of treatment, followed by crossover to the alternate treatment for an additional 6 to 7 days. The mean daily dose of ULTRESA was 6,270 lipase units per kilogram body weight per day. The mean exposure to ULTRESA during this study was 5.4 days.

The most common adverse reactions (≥7%) were headache, pharyngolaryngeal pain, and epistaxis. Table 1 enumerates adverse reactions that occurred in at least 2 patients (greater than or equal to 7%) treated with ULTRESA at a higher rate than with placebo in Study 1.

TABLE 1
Adverse Reactions Occurring in at Least 2 Patients (≥ 7%) in Cystic Fibrosis (Study 1)

Adverse Reaction	ULTRESA n=30 n (%)	PLACEBO n=31 n (%)
Headache	2 (7%)	1 (3%)
Pharyngolaryngeal Pain	2 (7%)	1 (3%)
Epistaxis	2 (7%)	0

Study 2 was an open-label study of 9 patients, ages 7 years to 11 years, with EPI due to CF. After a screening period of up to 15 days on individually-titrated doses of ULTRESA not to exceed 2,500 lipase units per kilogram per meal, patients entered a washout phase (no treatment) of up to 7 days before returning to a treatment phase of up to 12 days on the same individually-titrated dose of ULTRESA. Two patients discontinued during the washout phase leaving 7 patients in the treatment phase. The mean daily dose of ULTRESA was 6,361 lipase units per kilogram body weight per day during the last 4 days of the screening phase, and was 6,846 lipase units per kilogram body weight per day during the treatment phase. The mean duration of the treatment phase was 5.7 days.

Adverse reactions that occurred during treatment with ULTRESA were nasal congestion (14%), neck pain (14%), beta-hemolytic streptococcal infection (11%), ear pain (11%), and lymphadenopathy (11%).

6.2 Postmarketing Experience

Postmarketing data for ULTRESA has been available since 2003. The safety data is 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.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 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. ULTRESA 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.

8.3 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 ULTRESA 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.

8.4 Pediatric Use

The short-term safety and efficacy of ULTRESA were assessed in two clinical studies in pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis; one study included patients aged 8 years to 17 years, and the other included patients aged 7 years to 11 years.

Study 1 was a randomized, double-blind, placebo-controlled crossover study of 31 patients with exocrine pancreatic insufficiency due to cystic fibrosis including 2 children aged 8 to 11 years, and 12 adolescents aged 12 to 17 years. The safety and efficacy in pediatric patients in this study were similar to that in adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information]*.

Study 2 was an open-label study of 9 pediatric patients, ages 7 years to 11 years, with exocrine pancreatic insufficiency due to cystic fibrosis. Patients showed similar control of fat malabsorption as in the treatment arm of Study 1 *[see Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information]*.

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.

Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences. However, use of ULTRESA in children is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Attempting to divide the capsule contents in small fractions to deliver small doses of lipase is not recommended *[see Dosage and Administration (2)]*. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy and colonic strictures in children less than 12 years of age *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of ULTRESA 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.

10 OVERDOSAGE

There have been no reports of overdose in clinical trials or postmarketing surveillance with ULTRESA. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*. 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 (5.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase.

Marketed by:
Aptalis Pharma US, Inc.
22 Inverness Center Parkway
Birmingham, AL 35242 USA

Manufactured by:
Aptalis Pharma S.r.L.
Pessano, Italy 20060

MANAGED CARE NEWSSTAND

Infertility Treatment Can Worsen MS Symptoms

Women with multiple sclerosis (MS) who undergo assisted reproductive technology (ART) may increase their risk for MS symptoms. Researchers in Argentina compared MS disease activity in a small group of women with MS who had ART, MS patients who did not have ART, and a healthy group of women. They found that 75 percent of MS patients who had ART had exacerbations following ART. Nearly three-quarters of MS exacerbations were new symptoms and about one-quarter were a worsening of previous symptoms. ART also was associated with a nine-fold increase in disease activity on magnetic resonance imaging scans.

MS patients generally are not at increased risk for infertility unless they are receiving treatment with high-dose corticosteroids. The researchers noted, however, that reproductive hormones play a role in the development of autoimmune diseases.

The researchers say physicians should be aware of and discuss the risks and benefits of ART with women who have MS.

Source: Correale J, et al. Increase in multiple sclerosis activity after assisted reproduction technology. *Ann Neurol.* Epub ahead of print. Oct. 2012.

Stopping Asthma Medications May Not Be Right for Many Patients

Current asthma guidelines indicate that patients whose asthma is stable may be able to decrease or stop regular use of controller medications. But researchers say patients who choose to reduce their medication may increase their risk of exacerbations.

Researchers analyzed data from studies that compared the outcomes of asthma patients who continued use of low-dose inhaled corticosteroids with those who discontinued use of the medication. The seven studies included in the analysis involved patients who were stable for at least four weeks and who were followed up with for a period of three or more months.

They found that those who stopped taking medication were more than twice as likely to experience exacerbations as those who continued taking medication. The absolute risk of developing symptoms was 16 percent for those taking medication and 38 percent for those who discontinued corticosteroid therapy. Those no longer taking the low-dose steroids also had lower morning peak expiratory flow and increased asthma symptom scores.

This study supports a collaborative approach in which physicians and patients work together to find the lowest dose of medication needed to manage asthma symptoms effectively.

Source: Rank MA, et al. The risk of asthma exacerbation after stopping inhaled corticosteroids: A systematic review and meta-analysis. American College of Allergy, Asthma & Immunology 2012 Annual Scientific Meeting. Anaheim, California. Nov. 2012. Abstract 40.

Statins May Prevent Premature Cancer Deaths

Patients who take statins to lower their cholesterol may reap added health benefits. Danish researchers found that patients who took statins before they received a cancer diagnosis were less likely to die from cancer.

Researchers assessed the entire Danish population diagnosed with cancer between 1995 and 2007 and observed up to a 15 percent reduction in cancer-related mortality among those who were taking statins, compared with those who had never taken statins. The reduced mortality was noted in each of the 13 types of cancer studied.

The researchers say that by reducing the availability of cholesterol, statins may limit the cellular proliferation needed for cancer cells to grow and multiply. They call for clinical trials to help clarify the link between statins and cancer.

Source: Nielsen S, et al. Statin use and reduced cancer-related mortality. *N Engl J Med.* 2012;367:1792-1802.

Lifetime Risk of CVD Significant in All Adults

Even adults with optimal risk factor profiles for cardiovascular disease (CVD) have a good chance of developing CVD at some point in their lives. Researchers conducted a study to estimate lifetime risk for CVD, including coronary heart disease, congestive heart failure, stroke, and other causes of CVD deaths. They used data from the Framingham Heart Study and four other nationally funded studies. All participants were free of CVD when they entered the studies.

The researchers found that the lifetime risk for CVD was greater than 50 percent for adults in the United States. At age 55, men with no major risk factors had a 40 percent lifetime risk for CVD. Women of the same age with an optimal risk factor profile had about a 30 percent lifetime risk. Those with no risks developed CVD later in life than those who had risk factors.

The researchers say that their findings indicate the major public health burden of CVD. In addition, physicians may want to look for opportunities to prevent CVD even in those who have no major risk factors.

Source: Wilkins J, et al. Lifetime risk and years lived free of total cardiovascular disease. *JAMA.* 2012;308(17):1795-1801.

Pulmonary Hypertension Occurs Frequently in Patients with CKD

Researchers who recently looked at the association between chronic kidney disease (CKD) and pulmonary hypertension (PH) report in the *American Journal of Kidney Diseases* that patients with CKD frequently develop PH.

They found that the prevalence of PH ranges from 9 to 39 percent in those with stage 5 CKD; 18 to nearly 69 percent in patients on hemodialysis; and up to 42 percent in patients on peritoneal dialysis. There was no data for patients in the early stages of kidney disease.

Some of the factors that may aggravate or increase the risk for PH in patients with CKD include: left ventricular diseases, exposure to dialysis membranes, volume overload, endothelial dysfunction, an arteriovenous fistula, vascular calcification and stiffening, sleep-disordered breathing, and severe anemia.

The researchers say treating and preventing PH in patients with CKD is vital because even kidney transplantation may not alter the high mortality linked to PH. Although there have been no trials to evaluate interventions to reduce PH in CKD patients, researchers say correcting volume overload and treating left ventricular disorders is key to improving the outlook for CKD patients with PH.

Source: Bolignano D, et al. Pulmonary hypertension in CKD. *Am J Kidney Dis.* Epub ahead of print. Nov. 2012.

Biologics May Prevent Early Deaths in RA Patients

The biologic agents that help control pain and inflammation, prevent joint damage, and improve physical function may also reduce the risk for premature death in patients with rheumatoid arthritis (RA). Researchers from the University of British Columbia reviewed data on RA patients in Canada and compared patients who took biologics with biologic-naïve patients who had been treated with at least three disease-modifying anti-rheumatic drugs (DMARDs) and had changed therapy in the previous six months.

Researchers controlled for disease severity and other factors that may affect the risk for premature death and found that biologics reduced the risk for premature death by 25 percent when compared with patients who took no biologics.

The researchers say their results will help patients and physicians weigh the risks and benefits of the medications they choose to treat RA.

Source: Lacaille D, et al. Biologics may prevent premature death in people with rheumatoid arthritis. American College of Rheumatology Annual Meeting. Walter E. Washington Convention Center, Washington, D.C. Nov. 2012.

INTRODUCING

A new mechanism of action for OAB

The first and only FDA-approved β_3-adrenergic agonist

A new OAB therapy that targets a different pathway—the β_3-adrenergic receptor pathway

NEW

Myrbetriq™

(mirabegron)
extended-release tablets
25 mg, 50 mg

A new approach to OAB

Find out more at **MyrbetriqHCP.com**

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

Myrbetriq can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in severe uncontrolled hypertensive patients (defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg).

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Myrbetriq patients; however, Myrbetriq should be administered with caution to patients with clinically significant BOO. Myrbetriq should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB.

Since Myrbetriq is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with Myrbetriq. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone.

Most commonly reported adverse reactions (>2% and >placebo) for Myrbetriq 25 mg and 50 mg vs placebo, respectively, were hypertension (11.3%, 7.5% vs 7.6%), nasopharyngitis (3.5%, 3.9% vs 2.5%), urinary tract infection (4.2%, 2.9% vs 1.8%), and headache (2.1%, 3.2% vs 3.0%).

Please see Brief Summary of complete Prescribing Information on the adjacent page.

Printed in USA 012K-057-6780 November 2012

astellas

astellas

BRIEF SUMMARYOF PRESCRIBING INFORMATION
The following information is a brief summary only. See full prescribing information for MYRBETRIQ.

MYRBETRIQ™ (mirabegron) extended-release tablets

INDICATIONS AND USAGE

Myrbetriq is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

Increases in Blood Pressure

Myrbetriq can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg) *[see Clinical Pharmacology]*.

In two, randomized, placebo-controlled, healthy volunteer studies, Myrbetriq was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 3.5/1.5 mmHg greater than placebo.

In contrast, in OAB patients in clinical trials, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose of 50 mg was approximately 0.5 - 1 mmHg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in Myrbetriq patients.

Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Medications for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Myrbetriq patients; however, Myrbetriq should be administered with caution to patients with clinically significant BOO. Myrbetriq should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB *[see Clinical Pharmacology]*.

Patients Taking Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone *[see Drug Interactions and Clinical Pharmacology]*.

----------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 clinical practice.

In three, 12 week, double-blind, placebo-controlled, safety and efficacy studies in patients with overactive bladder (Studies 1, 2, and 3), Myrbetriq was evaluated for safety in 2736 patients *[see Clinical Studies]*. Study 1 also included an active control. For the combined Studies 1, 2, and 3, 432 patients received Myrbetriq 25 mg, 1375 received Myrbetriq 50 mg, and 929 received Myrbetriq 100 mg once daily. In these studies, the majority of the patients were Caucasian (94%), and female (72%) with a mean age of 59 years (range 18 to 95 years).

Myrbetriq was also evaluated for safety in 1632 patients who received Myrbetriq 50 mg once daily (n=812 patients) or Myrbetriq 100 mg (n=820 patients) in a 1 year, randomized, fixed dose, double-blind, active controlled, safety study in patients with overactive bladder (Study 4). Of these patients, 731 received Myrbetriq in a previous 12 week study. In Study 4, 1385 patients received Myrbetriq continuously for at least 6 months, 1311 patients received Myrbetriq for at least 9 months, and 564 patients received Myrbetriq for at least 1 year.

The most frequent adverse events (0.2%) leading to discontinuation in Studies 1, 2 and 3 for the 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia.

Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

Table 1 lists adverse reactions, derived from all adverse events, that were reported in Studies 1, 2 and 3 at an incidence greater than placebo and in 1% or more of patients treated with Myrbetriq 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of Myrbetriq patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 1: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With Myrbetriq 25 mg or 50 mg Once Daily in Studies 1, 2, and 3

	Placebo (%)	**Myrbetriq 25 mg (%)**	**Myrbetriq 50 mg (%)**
Number of Patients	**1380**	**432**	**1375**
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

*Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.

Other adverse reactions reported by less than 1% of patients treated with Myrbetriq in Studies 1, 2, or 3 included:

Cardiac disorders: palpitations, blood pressure increased *[see Clinical Pharmacology]*

Eye Disorders: glaucoma *[see Clinical Pharmacology]*

Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension

Infections and Infestations: sinusitis, rhinitis

Investigations: GGT increased, AST increased, ALT increased, LDH increased

Renal and urinary disorders: nephrolithiasis, bladder pain

Reproductive system and breast disorders: vulvovaginal pruritus, vaginal infection

Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with Myrbetriq 50 mg for up to 52 weeks in Study 4. The most commonly reported adverse reactions (>3% of Myrbetriq patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 2: Percentages of Patients with Adverse Reactions, Derived from all Adverse Events, Reported by Greater Than 2% of Patients Treated With Myrbetriq 50 mg Once Daily in Study 4

	Myrbetriq 50 mg (%)	Active Control (%)
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

In Study 4, in patients treated with Myrbetriq 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Myrbetriq 50 mg, and these markers subsequently returned to baseline while both patients continued Myrbetriq.

In Study 4, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with Myrbetriq 50 mg, Myrbetriq 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with Myrbetriq 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In a separate clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking Myrbetriq 100 mg as well as an herbal medication (Kyufu Gold).

Postmarketing Experience

Because these spontaneously reported events are from the worldwide postmarketing experience, from a population of uncertain size, the frequency of events and the role of mirabegron in their causation cannot be reliably determined.

The following events have been reported in association with mirabegron use in worldwide postmarketing experience:

Urologic: urinary retention *[see Warnings and Precautions]*

----------DRUG INTERACTIONS----------

Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives) *[see Clinical Pharmacology]*. No dose adjustment is recommended when these drugs are co-administered with mirabegron.

Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, Myrbetriq should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention *[see Warnings and Precautions].*

The following are drug interactions for which monitoring is recommended:

Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Myrbetriq is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions and Clinical Pharmacology]*.

Digoxin

When given in combination, mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Clinical Pharmacology]*.

Warfarin

The mean C_{max} of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated *[see Clinical Pharmacology]*.

----------USE IN SPECIFIC POPULATIONS----------

PREGNANCY

Pregnancy Category C

There are no adequate and well-controlled studies using Myrbetriq in pregnant women. Myrbetriq should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during Myrbetriq treatment are encouraged to contact their physician.

Risk Summary

Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures greater than or equal to 22 and 14 times, respectively, the maximal recommended human dose (MRHD). At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and fetal death, dilated aorta, and cardiomegaly were reported in rabbits.

Nursing Mothers

It is not known whether Myrbetriq is excreted in human milk. Mirabegron was found in the milk of rats at concentrations twice the maternal plasma level. Mirabegron was found in the lungs, liver, and kidneys of nursing pups. No studies have been conducted to assess the impact of Myrbetriq on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because Myrbetriq is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Myrbetriq in pediatric patients have not been established.

Geriatric Use

No dose adjustment is necessary for the elderly. The pharmacokinetics of Myrbetriq is not significantly influenced by age *[see Clinical Pharmacology]*. Of 5648 patients who received Myrbetriq in the phase 2 and 3 studies, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies.

Renal Impairment

Myrbetriq has not been studied in patients with end stage renal disease (CL_{cr} <15 mL/min or eGFR <15 mL/min/1.73 m^2 or patients requiring hemodialysis), and, therefore is not recommended for use in these patient populations.

In patients with severe renal impairment (CL_{cr} 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment (CL_{cr} 30 to 89 mL/min or eGFR 30 to 89 mL/min/1.73 m^2) *[see Clinical Pharmacology]*.

Hepatic Impairment

Myrbetriq has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), and therefore is not recommended for use in this patient population.

In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology]*.

Gender

No dose adjustment is necessary based on gender. When corrected for differences in body weight, the Myrbetriq systemic exposure is 20% to 30% higher in females compared to males.

OVERDOSAGE

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 bpm (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers. Treatment for overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

Pharmacodynamics

Urodynamics

The effects of Myrbetriq on maximum urinary flow rate and detrusor pressure at maximum flow rate were assessed in a urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and BOO. Administration of Myrbetriq once daily for 12 weeks did not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in this study. Nonetheless, Myrbetriq should be administered with caution to patients with clinically significant BOO *[see Warnings and Precautions]*.

Cardiac Electrophysiology

The effect of multiple doses of Myrbetriq 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 msec. For the 50 mg Myrbetriq dose group (the maximum approved dosage), the mean difference from placebo on QTcI interval at 4-5 hours post-dose was 3.7 msec (upper bound of the 95% CI 5.1 msec).
For the Myrbetriq 100 mg and 200 mg doses groups (dosages greater than the maximum approved dose and resulting in substantial multiples of the anticipated maximum blood levels at 50 mg), the mean differences from placebo in QTcI interval at 4-5 hours post-dose were 6.1 msec (upper bound of the 95% CI 7.6 msec) and 8.1 msec (upper bound of the 95% CI 9.8 msec), respectively. At the Myrbetriq 200 mg dose, in females, the mean effect was 10.4 msec (upper bound of the 95% CI 13.4 msec).
In this thorough QT study, Myrbetriq increased heart rate on ECG in a dose dependent manner. Maximum mean increases from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 beats per minutes (bpm), 11 bpm, and 17 bpm, respectively. In the clinical efficacy and safety studies, the change from baseline in mean pulse rate for Myrbetriq 50 mg was approximately 1 bpm. In this thorough QT study, Myrbetriq also increased blood pressure in a dose dependent manner (see *Effects on Blood Pressure*).

Effects on Blood Pressure

In a study of 352 healthy subjects assessing the effect of multiple daily doses of 50 mg, 100 mg, and 200 mg of Myrbetriq for 10 days on the QTc interval, the maximum mean increase in supine SBP/DBP at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mmHg greater than placebo. The 24-hour average increases in SBP compared to placebo were 3.0, 5.5, and 9.7 mmHg at Myrbetriq doses of 50 mg, 100 mg and 200 mg, respectively. Increases in DBP were also dose-dependent, but were smaller than SBP.

In another study in 96 healthy subjects to assess the impact of age on pharmacokinetics of multiple daily doses of 50 mg, 100 mg, 200 mg, and 300 mg of Myrbetriq for 10 days, SBP also increased in a dose-dependent manner. The mean maximum increases in SBP were approximately 2.5, 4.5, 5.5 and 6.5 mmHg for Myrbetriq exposures associated with doses of 50 mg, 100 mg, 200 mg and 300 mg, respectively.

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies (Studies 1, 2 and 3) in OAB patients receiving Myrbetriq 25 mg, 50 mg, or 100 mg once daily, mean increases in SBP/DBP compared to placebo of approximately 0.5 - 1 mmHg were observed. Morning SBP increased by at least 15 mmHg from baseline in 5.3%, 5.1%, and 6.7% of placebo, Myrbetriq 25 mg and Myrbetriq 50 mg patients, respectively. Morning DBP increased by at least 10 mmHg in 4.6%, 4.1% and 6.6% of placebo, Myrbetriq 25 mg, and Myrbetriq 50 mg patients, respectively. Both SBP and DBP increases were reversible upon discontinuation of treatment.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity

Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher in rats and 21 to 38-fold higher in mice than the human systemic exposure at the 50 mg dose.

Mutagenesis

Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility

Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22 times the MRHD in women and 93 times the MRHD in men.

PATIENT COUNSELING INFORMATION

Inform patients that Myrbetriq may increase blood pressure. Periodic blood pressure determinations are recommended, especially in patients with hypertension. Myrbetriq has also been associated with infrequent urinary tract infections, rapid heart beat, rash, and pruritus. Inform patients that urinary retention has been reported when taking mirabegron in combination with antimuscarinic drugs used in the treatment of overactive bladder. Instruct patients to contact their physician if they experience these effects while taking Myrbetriq.

Patients should read the patient leaflet entitled “Patient Information” before starting therapy with Myrbetriq.

Rx Only

PRODUCT OF JAPAN

Manufactured by:

Astellas Pharma Technologies, Inc.

Norman, Oklahoma 73072 Marketed

and Distributed by:

Astellas Pharma US, Inc.

Northbrook, Illinois 60062

Revised: September 2012
2H055-MIR-BRFS

012J-056-6594

Immune Globulin Therapy:
Appropriate Management and Managed Care Implications

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Therapeutic Uses of Immune Globulin Therapy

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Although immune globulin (Ig) therapy is used to treat more than 100 disease states, there are only four indications currently approved by the U.S. Food and Drug Administration (FDA): primary immunodeficiency disease (PIDD), idiopathic thrombocytopenic purpura (ITP), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN). Previously approved indications include Kawasaki syndrome and chronic lymphocytic leukemia (CLL); however, the specific products approved for these indications are no longer on the market. The use of intravenous immune globulin (IVIg) therapy in North America has grown, on average, 11 percent per year, and is steadily increasing as it continues to be used for more indications.[1] Off-label use constitutes about 50 to 80 percent of total Ig utilization.[2] The most common off-label indications include multiple sclerosis, graft-versus-host disease in transplant recipients, prevention of antiphospholipid syndrome in miscarriage, and Guillain-Barre syndrome.[3] Ig therapy may be useful in numerous conditions, but evidence supporting its efficacy is mixed (Table 1).[3] The largest share of Ig therapy use belongs to patients with neurological conditions, followed by primary immunodeficiency disorders (Figure 1, page 20).[3] Currently, there are several ongoing clinical trials that are evaluating new uses for Ig therapy, including Alzheimer's disease (AD), autism spectrum disorder (ASD), complex regional pain syndrome, and *Clostridium difficile* infection (CDI).

The Economic Burden of Immune Globulin Therapy

The management of Medicare patients on Ig therapy has shifted away from physician offices due to reimbursement changes; an estimated 42 percent of patients are referred to other locations for administration.[4] Although hospitals

Table 1

Off-Label Use of Immunoglobulin Therapy[3]

Efficacy confirmed in randomized controlled trials	Probable effectiveness	Possible effectiveness	Doubtful effectiveness
Guillain-Barre syndrome in adults	Polymyositis Dermatomyositis Autoimmune uveitis Stiff-person syndrome Myasthenia gravis Guillain-Barre syndrome in children Toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome	Severe persistent asthma Post-transfusion purpura Autoimmune hemolytic anemia Autoimmune hemophilia Autoimmune neutropenia Lambert-Eaton syndrome Multiple sclerosis Connective tissue diseases and systemic vasculitis Churg-Strauss syndrome Autoimmune blistering diseases Chronic urticaria Systemic lupus erythematosus Neonatal alloimmune thrombocytopenia	Inclusion body myositis Antiphospholipid antibody syndrome in pregnancy Chronic fatigue syndrome Immunodeficiency associated with adult HIV infection Miller Fisher syndrome Recurrent spontaneous abortion

have received most of these patients, payment issues still present a barrier to the standard of care. Medicare reduced reimbursement rates for Ig therapy with the introduction of the average sales price (ASP) methodology. Some healthcare providers are paying more than the ASP plus 6 percent for IVIg and are not fully reimbursed. Table 2 (page 20) includes the Medicare Part B payment allowance limits, which indicates the ASP for the products listed by the Centers for Medicare & Medicaid Services (CMS).[5] An Immune Deficiency Foundation (IDF) survey of hospital pharmacy directors showed that 32 percent of hospitals reported turning away patients requiring IVIg in 2006 as a result of reimbursement issues.[6] In addition, a physician survey conducted jointly by the IDF and the American Academy of Allergy, Asthma, and Immunology (AAAAI) reported that 39 percent of physicians had to reduce the frequency of IVIg infusion and 26 percent had to decrease the average IVIg dose of their patients with PIDD due to changes in payment structure.[7] As a result, patients had experienced additional or more severe health problems according to 38 percent of physicians who answered the survey.[7]

Due to the lack of one specific comprehensive treatment guideline and the use of Ig therapy for a plethora of disease states, the economic burden is significant for managed care. As the use of Ig therapy expands with more FDA-approved and off-label utilization, healthcare expenditures continue to rise exponentially. The average annual cost for Ig therapy can range from $30,000 to $90,000 per patient depending on dose, infusion time, length of treatment, and site-of-care.[8] Due to lack of supporting clinical evidence, the inappropriate use of Ig therapy is contributing to an unnecessary burden on the healthcare system. When used appropriately, Ig therapy has been shown to be clinically, as well as economically, beneficial. For example, if PIDD is left untreated, the annual cost reaches more than $140,000 per patient due to

The use of intravenous immune globulin (IVIg) therapy in North America has grown, on average, 11 percent per year, and is steadily increasing as it continues to be used for more indications.[1]

Figure 1 **Ig Therapy Use by Medical Specialty in 2012[3]**

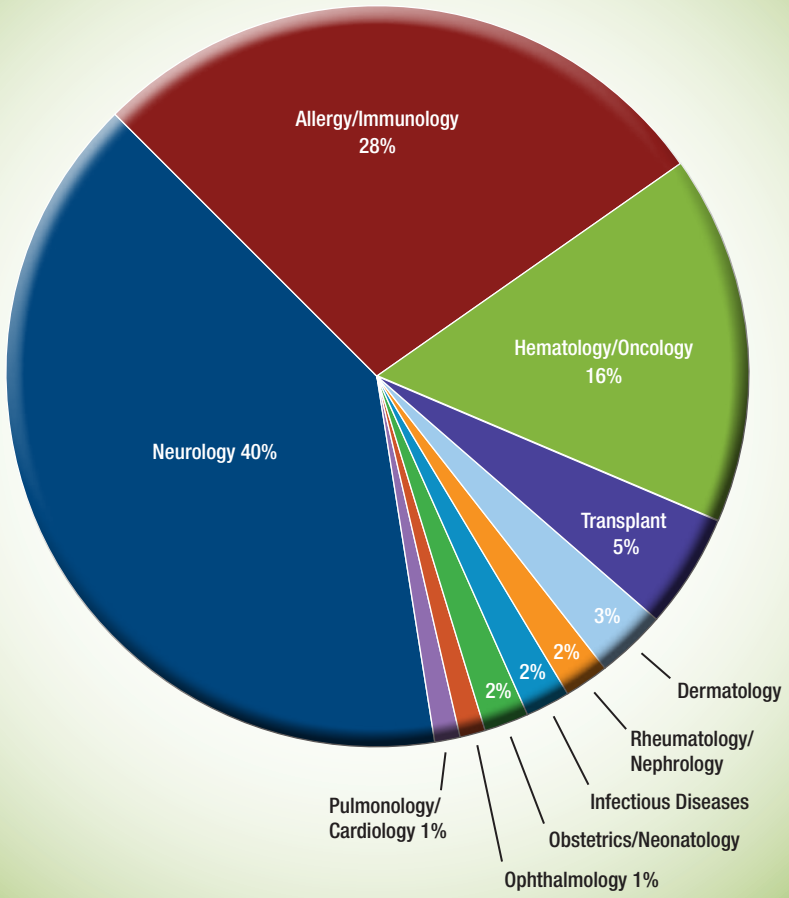

Table 2 **Payment Allowance Limits for Medicare Part B Drugs[5]**

HCPCS Code	Drug Name	HCPCS Code Dosage	ASP + 6% Listed by CMS
J1459	Privigen	500 mg	35.569
J1557	Gammaplex	500 mg	36.592
J1559	Hizentra	500 mg	36.430
J1561	Gamunex-C/Gammaked	500 mg	38.231
J1566	Immune globulin, powder	500 mg	34.735
J1568	Octagam	500 mg	31.599
J1569	Gammagard Liquid	500 mg	37.637
J1572	Flebogamma	500 mg	34.945

infections, hospitalizations, antibiotic utilization, and school/work days missed[8]. Conversely, annual cost-savings of $78,000 per patient have been seen if Ig therapy is utlized.[8]

To ensure prudent, safe, and effective use of Ig therapy, it is important to have a collaboration of specialists and managed care executives to accurately define individual indications along with specific guidelines and criteria for Ig use. Most organizations have prior authorization criteria in place for the use of Ig therapy; however, some managed care organizations (MCOs) have taken a liberal approach, while others have left no flexibility for physicians. There is a need for a streamlined approach to managing the use of Ig therapy in order to minimize improper utilization while ensuring access for appropriate candidates.

Formulary Management

Since there are currently 10 Ig products licensed for use in the United States, there is an opportunity for cost-savings through formulary management. Tables 3 and 4 summarize the products for intravenous and subcutaneous administration, respectively. After considering efficacy and safety, contracting for preferred Ig products among those that are clinically similar has the potential to achieve considerable cost-savings.[9] With the increasing number of Ig products available on the U.S. market from various manufacturers, the potential for competitive contract negotiation is significant. All currently available agents contain the active ingredient immune globulin G (IgG), but there

are differences between the products, such as sodium content, stabilizers, osmolality, osmolarity, immune globulin A content, infusion rates, concentration, and pH.[9] While there have not been direct-comparison clinical trials between Ig products to date, it is generally agreed that all Ig products are clinically comparable and therefore interchangeable. The specific pharmaceutical qualities of the various products are what differentiate them, as patient tolerability can vary widely from product to product.[10] For MCOs evaluating cost-saving opportunities through formulary management, it may be appropriate to consider adding products that have a 5 percent and 10 percent concentration so that providers have options, especially for those patients who cannot tolerate one or the other.

There are numerous cost issues that need to be considered when deciding which Ig therapy will be on formulary. For example, lyophilized products have a low acquisition cost; however, liquid products offer more savings because they do not require special admixture facilities, technician labor, and pharmacist supervision.[9] This problem may not be as prominent anymore since lyophilized products are now being discontinued by manufacturers as new liquid products are coming into the market. Some Ig products, such as Gammagard Liquid by Baxter, have several vial sizes, including 1g, 2.5g, 5g, 10g, 20g, and 30g, while Gammaplex by Bio Products Laboratory has only 5g and 10g. Selecting products that have various vial sizes is essential to avoid waste. If an institution has many pediatric patients who need IVIg, a significant amount of waste will be generated per patient if the smallest vial size on the formulary is 5g. Dose rounding can mitigate waste; however, it is important to have different vial sizes available to minimize long-term, accumulative waste.

There is a substantial opportunity for cost-savings with Ig therapy, but clinical, operational, and purchasing considerations need to be evaluated when determining the appropriate formulary.[9]

Intravenous vs. Subcutaneous Administration

Much data exists comparing treatments and costs between intravenous and subcutaneous administration. A summary of the key differences is highlighted in Table 5 (page 23). Studies in the United States have found that switching from IVIg to SCIg achieved higher IgG levels and reduced infections, hospitalizations, days on antibiotics, and rate of work/school days missed.[12] In Sweden, a study calculated a savings of $10,000 per patient per year with subcutaneous administration.[14] Other factors to consider when comparing SQ and IV administration are indirect costs,

Table 3

Intravenous Immune Globulin Therapy[11]

Brand Name	Gammagard Liquid	Gammaplex	Gamunex-C	Gammaked	Privigen	Carimune	Octagam	Flebogamma	Bivigam
Manufacturer	Baxter	Bio Products Laboratory	Talecris Biotherapeutics		CSL Behring		Octapharma USA	Instituto Grifols	Biotest Pharmaceuticals
FDA-Approved Indications	PIDD, MMN	PIDD, ITP, CIDP	PIDD, ITP, CIDP		PIDD, ITP	PIDD, ITP	PIDD	PIDD	PIDD
PRODUCT CHARACTERISTIC									
Formulation	10% Liquid	10% Liquid	5% Liquid	10% Liquid	10% Liquid	Lyophilized for reconstitution to 3–12%	5% Liquid	5% and 10% Liquid	10% Liquid
Vial Sizes (in grams)	1, 2.5, 5, 10, 20, 30	1, 2.5, 5, 10, 20	5, 10	1, 2.5, 5, 10, 20	5, 10, 20	3, 6, 12	1, 2.5, 5, 10, 25	0.5, 2.5, 5, 10, 20	5, 10

Table 4

Subcutaneous Immune Globulin Therapy[11]

Brand Name	GAMMAGARD LIQUID	HIZENTRA	GAMUNEX-C	GAMMAKED
Manufacturer	Baxter	CSL Behring AG	Talecris Biotherapeutics	
FDA-Approved Indications for SC Use	PIDD			
PRODUCT CHARACTERISTICS				
Formulation (concentration)	10% Liquid	20% Liquid	10% Liquid	
Vial Sizes (in grams)	1, 2.5, 5, 10, 20, 30	1, 2, 4	1, 2.5, 5, 10, 20	
ADMINISTRATION CONSIDERATIONS				
Average SC dose adjustment required to achieve equivalent of IVIg dose in clinical trials	137%	153%	137%	
Initial SC dosing Note: Dose should be individualized based on the patient's clinical response to therapy (primary consideration) and serum IgG trough levels.	Initial dose = 1.37 x previous IVIg dose (g)/ No. of weeks between IVIG doses	Initial dose = 1.53 x previous IVIg dose (g)/ No. of weeks between IVIg doses	Initial dose = 1.37 x previous IVIg dose (g)/ No. of weeks between IVIg doses	

such as travel time, pre-medications, supplies needed for infusion, and unused waste. European economic studies performed in Sweden, Germany, the U.K., and France reported that home-based SCIg was 25 to 75 percent less costly for the healthcare system than hospital-based IVIg.[15] A Canadian study reported a cost difference of <10 percent between the two options.[15] Unfortunately, these cost-savings cannot be correlated with those in the United States, since the cost of immunoglobulin products varies in different countries.

Although there are advantages of SCIg, potential limitations to its use exist. There is a notion that the total area under the curve (AUC) of SCIg products is reduced compared with the AUC achieved with equivalent doses of IVIg in the same patients. Therefore, it is recommended by the FDA that the SCIg dose in the United States be 137 percent to 153 percent of the IVIg dose to achieve an equivalent AUC.[16] While the clinical relevance of AUC differences remains unproven, it is a confounder that adds to cost calculations, which has become an issue for regulators in the United States.[16] European regulators do not consider AUC equivalence to be relevant for clinical response, and recommend dosing of SCIg at 100 percent of the IVIg dose.[16]

From a patient perspective, the autonomy associated with home-based SCIg administration translates into improved quality of life. Although SCIg is typically administered weekly by an infusion pump, administration by a rapid-push technique may provide a greater degree of convenience. SCIg delivered by rapid push has been shown to be preferred by adult PIDD patients who were given the choice.[16,17] Hence, in addition to increased patient autonomy and shorter infusions, rapid-push SCIg provides an improved option for patients and results in significantly reduced cost for the healthcare systems of various countries.[15] Although existing evidence suggests cost-savings with utilization of SCIg, healthcare economics vary markedly among countries and, therefore, comparative studies in the United States need to be conducted in order

Hence, in addition to increased patient autonomy and shorter infusions, rapid-push SCIg provides an improved option for patients and results in significantly reduced cost for the healthcare systems of various countries.[15]

to determine whether SQ or IV administration is more cost-effective.

Appropriate Dosing

Prescribing the proper dose of Ig therapy presents a significant challenge for providers, especially for off-label use. Physicians often rely on professional judgment, along with peer-reviewed literature and clinical assessment, to determine the dose (Table 6, page 24).[19] In the past, it was discovered that doses between 150 mg/kg to 250 mg/kg were not adequate to raise the IgG trough level to a goal of > 600 mg/dL, which correlated with clinical response.[20] Hence, doses as high as 500 mg/kg were being used. With expanded utilization including ITP, CIDP, and Kawasaki syndrome, doses as high as 2g/kg are currently being prescribed. High-dose IVIg is generally well-tolerated, but there are reports of hemolytic anemia induced by anti-blood group antibodies present in IVIg.[21] In addition, fluid volume, protein load, and glucose tolerance can become significant patient concerns with high-dose IVIg. According to many experts, clinical response can be achieved with lower doses of IVIg than what is currently being prescribed for several disease states.

There is much discussion regarding the weight that should be used when determining IVIg dosing. In order to minimize cost and waste, Jerry Siegel, PharmD, FASHP, expert IVIg clinical pharmacist and Senior Director of Pharmaceutical Services at Ohio State University Medical Center, has developed an algorithm to determine the best dosing weight that should be used to provide the

Table 5

Intravenous vs. Subcutaneous Administration[18]

	Intravenous Route	Subcutaneous Route
Pharmacokinetics	Wide difference in serum IgG level between peak and trough	Consistent serum IgG levels
Efficacy	Long clinical experience demonstrating efficacy	Two prospective trials demonstrate noninferiority compared to IVIg
Systemic side effects	Common	Infrequent
Infusion site reactions	Infrequent	Common
Factors contributing to total cost	Typically administered in an infusion center with nursing support	Self-administered at home. U.S. trials of previously available vivaglobin suggested using a higher dose (1.37x) than IVIg.
Patient satisfaction	Often a better option for patients who have difficulty with needles and/or self-injection. Preferable in patients who have difficulty with compliance.	Offers a multiple of infusion frequency, site, etc. Multiple studies confirm enhanced quality of life in PIDD.

Advantages	
Achieve rapid plasma levels	Option for patients with poor venous access
Available route for patients with bleeding disorders	Eliminates trough levels and provides stable serum levels of IgG
Dosing interval usually every 3 to 4 weeks	May offer less systemic AEs than IV route
Greater compliance monitoring opportunity for clinic- or hospital-based IVIg infusion settings	Increased flexibility for patient's or parent's schedule, especially since rapid push is available
	May be associated with lower costs compared to hospital-based IVIg
Disadvantages	
Need intravenous access	Increased local reactions at the site of infusion
Patient infusion time commitment and schedule interruption for 3 to 5 hours every 3 to 4 weeks	Requires good patient reliability and compliance
Often requires travel to a hospital or infusion center	Need for a pump, home care technique instructions
Increased systemic reactions	Although more conveniently given at home, infusions given more often (weekly)
	Limited option for patients with decreased dexterity

Table 6 **Dosing Recommendations for All U.S.-Approved Immune Globulin Products[19]**

Product	Manufacturer	Indication	Administration Route	Dosing Recommendations
Carimune NF	CSL Behring	PIDD	IV	0.4 to 0.8 g/kg every 3 to 4 weeks
		ITP	IV	0.4 g/kg over 2 to 5 consecutive days
Flebogamma DIF 5%	Grifols	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Flebogamma DIF 10%	Grifols	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Gammagard Liquid	Baxter	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
		MMN	IV	0.5 to 2.4 g/kg/month
		PIDD	SC	Initial Dose: 1.37 x previous IVIg dose (in grams)/No. of weeks between IVIg doses
Gammaplex	Bio Products Laboratory	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Gamunex – C	Talecris Biotherapeutics	PIDD	SC	Initial dose: 1.37 x previous IVIg dose (in grams)/No. of weeks between IVIg doses
		PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
		ITP	IV	2 g/kg
		CIDP	IV	Loading dose: 2 g/kg Maintenance dose: 1 g/kg every 3 weeks
Hizentra	CSL Behring	PIDD	SC	Initial dose: 1.53 x IVIg dose (in grams)/No. of weeks between IVIg doses
Privigen	CSL Behring	PIDD	IV	200 to 800 mg/kg every 3 to 4 weeks
		ITP	IV	1 g/kg IV daily for 2 consecutive days (2 g/kg total)
Octagam 5%	Octapharma	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Bivigam	Biotest Pharmaceuticals	PIDD	IV	300 to 800 mg/kg every 3 to 4 weeks

most effective treatment in a cost-efficient manner.[20] Many healthcare policies also carry a clause in which the physician must try a lower dose of Ig therapy to see if maintenance can be attained at a lower cost. Further studies are needed to establish standard dosing protocols for the various uses of Ig therapy.

Choosing a Preferred Site-of-Care

Another opportunity for MCOs to reduce costs is through the utilization of a preferred site-of-care for Ig infusion services, as well as other therapies. There are many advantages to using preferred sites-of-care (i.e., home infusion, doctors' offices, and infusion clinics) that are all linked to an increase in patients' quality of life and a reduction in healthcare burden. The AAAAI site-of-care guidelines recommend that all initial infusions of Ig therapy be provided under physician supervision in a facility equipped to handle the most severe acute medical complications,[22] since the majority of Ig-related adverse events occur during the first infusion or during a change from one Ig product to another.[22] Once patients have tolerated Ig therapy, preferred site-of-care settings should be considered.[22] The subcutaneous route greatly facilitates home therapy; Berger and colleagues estimate a savings of $2,000 to $5,000 per patient per year by avoiding the facility costs associated with infusions.[23] Although it is best to recommend a preferred site-of-care setting for appropriate patients on chronic Ig therapy, it is also important to note that patient experience, flexibility, and support may mandate or preclude specific sites-of-care.[22]

Managed Care Considerations

Although there are a few consensus guidelines published to date, there is a need for standards that can be adopted in the United States. Careful consideration of appropriate use needs to be incorporated into policies after reviewing evidence-based studies. One valuable resource to help guide physicians when prescribing IVIg or SCIg is an article published by the PID committee of the AAAAI, "Practice Paper on the Appropriate Use of Intravenously Administered Immunoglobulin." Ig therapy is highly individualized, but utilization reviews can be helpful in identifying trends and inappropriate use. For example, SCIg may seem to be more expensive due to the conversion factor; however, providers within a network may already be using 1:1 conversions for their patients. Key experts in the field of Ig therapy can also be a tremendous resource to health plans for formulary management, as well as peer-to-peer discussions. Experts can be especially valuable in balancing formulary decisions to allow for cost-savings while maintaining clinically adequate options.

Ig therapy presents a growing challenge to healthcare organizations. Evidence-based literature and expert advice are instrumental in managing appropriate use of Ig therapy. Additionally, formulary compliance and site-of-care optimization can offer additional options for cost-effective management of Ig therapy.

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Assisted Reproductive Technology and Managed Care: Managing the Cost and Risks

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Assisted reproductive technology (ART) has revolutionized the area of infertility treatment, enabling thousands of couples to reach their goals of pregnancy and birth. Yet despite the identification of infertility as a disease by the American Society for Reproductive Medicine (ASRM), it is still considered an area of high cost and a quality-of-life issue by payors and employers. Thus, insurance coverage for the procedure is limited, with just 15 states requiring such coverage.[1]

This makes ART one of the few areas of medicine that operates in the open marketplace. The growth of the ART industry in the United States, with more than 400 centers currently operating, has created significant competition to demonstrate high pregnancy and live-birth rates. This, in turn, has resulted in high rates of multiple births, which drives up costs even for health plans that do not cover ART procedures. However, health plans have the opportunity to address this problem and reduce costs associated with ART.

Reducing the Cost and Burden of ART Coverage

Although studies find that the use of preauthorization and capitation, as well as certain contractual arrangements with clinicians, can reduce the cost of ART for health plans, the greatest cost reduction comes from reducing multiple births.[6,7]

In 2008, more than 3 percent of all births in the United States were multiples, the majority of which could be traced back to ART. Between 1998 and 2008, for instance, the twin birth rate rose from 2.8 to 3.4 percent, even as the success rate of in-vitro fertilization (IVF) with a single-embryo transfer (SET) increased. In addition, the majority of triplets and higher-order multiples result from ART.[8] These multiple births occur not only from returning two or more embryos during IVF, but primarily from controlled ovulation stimulation (COS)/intrauterine insemination (IUI).[9] COS is the induction of ovulation using fertility drugs to produce more than one mature follicle per cycle, releasing multiple eggs. This is often used in conjunction with IUI. It is important to note that the rate of triplets associated with IVF has decreased by more than 50 percent, but this same trend has not been observed in patients receiving COS.

Payors often require a stepped approach to fertility treatments, requiring at least one COS/IUI prior to IVF. However, not only are higher-order multiples (triplets and quadruplets) more likely with COS/IUI than with IVF, but the procedure itself also carries a greater risk of potentially fatal—and medically expensive—ovarian hyperstimulation.[10-12]

Additionally, one study found that a single cycle of IVF resulted in a higher live birth rate than three cycles of COS/IUI, while another found a twofold increased success rate with IVF.[11,12]

There is also evidence that a full IVF cycle is less costly and more cost-effective than IUI with or without COS in couples with unexplained infertility or mild male-factor infertility.[12,13]

Payors, employers, and benefit managers may wish to examine their benefit designs as well as coverage policies regarding the continuum of infertility treatment options as one opportunity to reduce the risk of high-cost multiple births and the number of fertility-related procedures.

Single-Embryo Transfer (SET)

The main reason for multiple births with ART is the transfer of more than one embryo during the procedure. The costs associated with multiple births affect all payors, regardless of coverage policies.

When comparing single cycles, double-embryo transfer (DET) produces a greater rate of pregnancies, per procedure, when compared to SET. However, in younger patients with an abundance of healthy embryos, an equivalent cumulative rate of pregnancies might be achieved using SET, while limiting the risk of multiples. Additionally, SET is usually associated with a different cost profile, which allows for cryopreservation; this has a different clinical value in younger patients compared to older patients (ages 37-39). This highlights the need to understand age and clinical profile in defining an appropriate treatment pathway that maximizes successful pregnancy outcomes, reduces multiple gestations, and reduces overall cost.

One prospective study of 151 women younger than age 36 undergoing IVF found a twin delivery rate of 3.5 percent in the SET group (n=53) compared to a 37.5 percent rate in the DET group (n=98) ($P<0.05$). However, there was no difference in the cumulative delivery rate per patient between the two cohorts. Neonatal outcomes in the twin cohort was, as might be expected, poorer than in the singletons.[15]

Potential Cost-Savings: Diagnose Infertility Quicker

Another potential area of cost-savings lies in improving the initial infertility workup women receive, something that nearly all health plans cover as part of their basic medical benefit. The American Society of Reproductive Medicine (ASRM) recommends that such evaluations "should be conducted in a systematic, expeditious, and cost-effective manner so as to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility."[31]

However, the average time from the start of infertility assessment to the final diagnosis is approximately one year, resulting in increased office visits, tests, and costs. Yet experienced clinicians can complete such workups in one month, or the duration of one menstrual cycle, to identify ovulatory dysfunction, the most common cause of infertility. Once identified, no further workup is required, unless a woman fails to conceive after three to six cycles of successful ovulation induction. In addition, clinical guidelines recommend that the sperm donor be evaluated simultaneously, rather than consecutively, as is often the case.[31]

The guidelines also limit laparoscopy to women with evidence of or a strong suspicion of advanced stages of endometriosis, tubal occlusive disease, or significant adnexal adhesions.[31] Yet many women needlessly undergo these invasive and costly procedures even without such indications.

Educating clinicians and members regarding the appropriate steps for an infertility workup to ensure a quicker, more cost-effective diagnosis could help health plans reduce their fertility-related costs.

Fertility Knowledge Among Physicians and Women 25 to 35: Implications for Health Plans

The first national survey assessing fertility knowledge among women ages 25 to 35 found that while seven out of 10 plan to have children, they do not plan to have their first child until they are in their early 30s—an average of seven years later than their own mothers.[32] Other results from the study of 1,001 women and a similar survey of 429 reproductive healthcare providers are highlighted below.

■ Most women believe that it is easier to get pregnant than it actually is and are unaware that even in their early 30s, they have a higher risk of infertility than in their 20s. They are also unaware that IVF success is tied to the age of the egg donor.

- Implication for health plans: Educate members about the increased risk for infertility with age, highlighting the fact that the longer women put off pregnancy, the greater their risk of infertility. Also educate women regarding success rates of IVF at different ages. There is also opportunity to educate on other factors, including sexually transmitted diseases, prevention, and screening recommendations.

■ Two out of three women are unfamiliar with hormonal fertility injections, and the majority tend to overestimate the success rate of IVF.

- Implication for health plans: Controlled ovarian stimulation, while less expensive than IVF, has a higher risk of multiples and ovarian hyperstimulation, with a similar or lower rate of success. Provide educational tools to members regarding the risks and benefits of each, as well as their success based on age and risk factors.

■ Women's preferred and primary source of fertility information is their OB/GYN. However, they rarely discuss their pregnancy plans, age as an infertility risk factor, or infertility treatment options with their doctor. In addition, a survey of OB/GYN and fertility healthcare providers found that they were not always aware of how much their patients knew about fertility issues.[33]

- Implication for health plans: Educate OB/GYNs regarding the importance of such discussions and education. Consider including as part of wellness and prevention to encourage OB/GYNs to provide such education to their patients.

■ Healthcare providers overestimate patient awareness of fertility information, including their knowledge of the risk of multiple births with assisted reproductive technology (ART).

- Implication for health plans: Educate members with infertility about the risks for multiple births with IVF as a way to minimize the substantial costs and risks associated with a multiple pregnancy.

There is also good evidence that SET is more cost-effective than DET, primarily because of the savings resulting from singleton vs. multiple births.[16]

The costs of a multiple pregnancy vs. a singleton pregnancy are staggering. Twin pregnancies cost four to five times that of singleton pregnancies, and triplet pregnancies result in a tenfold increase.[8,21] The high rate of preterm births resulting from ART, primarily because of multiple pregnancies, cost the United States approximately $1 billion in 2004 alone.[22]

A Belgium study found that three months after birth, the total average cost for a DET birth was twice that of an SET ($11,389 vs. $6,214; P=0.016), with the additional cost due entirely to higher neonatal costs from twins.[16] A Finnish study found similar results, with healthcare costs for an IVF singleton throughout the neonatal period of $7,537 vs. $20,601 for IVF twins.[23]

Meanwhile, a U.S. study found hospital charges of $16,009, $61,704, and $1.8 million for singleton, twin, and triplet births, respectively. Those amounts are likely higher since they were converted from 1991 to 2011 dollars based on the inflation rate, yet healthcare costs in this country have grown far faster than the rate of inflation.[24] In addition, multiples, who often develop long-term sequelae from prematurity and time spent in the neonatal ICU, have higher lifetime medical and educational costs, many of which insurance plans bear.[8]

Despite evidence of similar pregnancy rates between SET and DET, however, most clinics in the United States transfer more than one embryo in the majority of IVF cycles, with SET accounting for just 12

Table 1 Average Number of Embryos Transferred in 2010 Based on Woman's Age

Age	<35	35-37	38-40	41-41	43-44	>44
Average number of embryos transferred	2.0	2.2	2.6	3.0	3.2	2.7

Source: Centers for Disease Control and Prevention. Assisted Reproductive Technology (ART) Report. Accessed 1 Feb. 2013 at http://apps.nccd.cdc.gov/art/Apps/NationalSummaryReport.aspx.

percent of all embryo transfers in 2009.[25] Table 1 shows the average number of embryos transferred in 2010 based on the woman's age.

The ASRM recommends a single blastocyst or one to two cleavage-stage embryo transfers for women younger than age 35 with "favorable" indicators (first IVF, good-quality blastocysts, other embryos for cryopreservation, or previous successful IVF). All other women in that age group should have no more than two embryos transferred, while older women may have from two to five embryos transferred, depending on their age, medical history, and the quality of the embryos.[26]

There are several reasons for the low uptake of SET in the United States:

- The desire of fertility clinics to maximize pregnancy and live birth rates. Such data is reported annually to the Centers for Disease Control and Prevention. It is freely available on the Internet to potential patients, who often choose a clinic based on its pregnancy and live birth rate without understanding the risks of a multiple pregnancy.
- Patient desire to maximize the likelihood of pregnancy while minimizing the risk of multiple cycles. One study found that at least 20 percent of infertile couples prefer multiples over a singleton pregnancy, particularly those with little knowledge of the risks of multiple births.[27] However, educating IVF couples about the risks of singletons vs. twins can significantly increase the number of couples opting for single-embryo transfer, resulting in a lower rate of multiples with no difference in overall pregnancy rates.[27]
- The availability of insurance coverage. Reproductive clinics in states with mandated coverage of ART transfer fewer embryos per cycle than clinics in states without mandates, regardless of the woman's age.[9,28] Such mandates result in fewer multiple births per transfer and births per cycle in women younger than age 35, and lower multiple birth rates in women ages 38 to 40.[9,29]

Opportunities to Increase the Success of Single-Embryo Transfer

The use of certain technologies, such as comprehensive chromosome screening (CCS), which screens for abnormalities in 24 chromosomes, can improve the success rate of SET as well as reduce miscarriages.[30] The procedure involves testing the chromosomal number in blastocysts, then transferring one or more with a normal set of chromosomes. This is important since only about 3 percent of IVF embryos are of sufficient quality to be transferred and, of those, only about 12 percent will result in a live birth.

A recent study of 140 patients who had SET after CCS found an ongoing pregnancy rate of 55 percent, compared to the 41.8 percent rate in an unscreened SET cohort. This higher rate occurred even though the CCS women were older and had a greater rate of miscarriage in early pregnancy.[30]

Genetic screening can also identify patients whose eggs will have a very low probability to achieve a viable pregnancy and accelerate the process of identifying who will need egg donation. This can also be a cost-savings strategy for plans by reducing the number of failed cycles. In addition, plans that encourage SET might also consider limiting the procedure to two trials; most women with viable eggs will become pregnant the first time, but nearly all will be successful with two IVF cycles.

In addition, couples can maximize their chance of a pregnancy by using frozen embryos, since a typical IVF cycle may result in multiple high-quality blastocysts that can be safely frozen, thawed, and used for subsequent cycles, although the success rate is lower.

Despite the promise of better outcomes, the value of universal preimplantation genetic screening (PGS) is still debatable in the literature and is not supported by the ASRM. However, for high-risk patients with chromosomal abnormalities of repeated miscarriages, the selection of euploid embryos for transfer has shown to increase pregnancy rates with a low incidence of miscarriage.

Thus, as promising new technologies emerge, payors must weigh whether there is enough evidence to support new technology that may improve outcomes, limit the number of IVF cycles, reduce multiples, and limit the attendant short- and long-term costs of multiple births. In the end, it is important to look beyond the initial cost of infertility treatment and analyze the total cost of a "successful" procedure, particularly if that procedure involves multiple gestations.

Conclusion

The rise in multiple births in this country over the past 30 years and the concurrent increase in preterm births is due entirely to ART.[8] When the field began in 1980, the technology was crude and our understanding of the processes elementary. Thus, transferring two or more embryos in order to maximize pregnancy and live birth rates became the norm. However, despite significant improvements in ART technologies that can provide similar pregnancy rates with SET while nearly eliminating the medical and economic costly consequences of multiple-embryo transfers, the majority of clinicians in this country continue to transfer more than one embryo.

The medical costs of this misguided approach are staggering, whether or not health plans cover the initial IVF procedure. While some countries mandate SET for most IVF procedures, this might be going too far. A more appropriate and measured approach would be for payors, which bear the economic brunt of multiple births, to improve patient and clinician education, as well as gain insight into best practices and a better understanding of how integrating pharmacy-medical benefit design and coverage policies can impact outcomes and cost.

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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 ≥7% and ≤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®

Levemir® FlexPen®
insulin detemir (rDNA origin) injection

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

novo nordisk®

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 lipoatrophy (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.

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Revised: 1/2012

0212-00007333-1 2/2012

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insulin detemir (rDNA origin) injection

Current and Future Managed Care Considerations for the Treatment of Castration-Resistant Prostate Cancer

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Prostate cancer is the second-leading cause of cancer-related deaths in American men and is estimated to cost the U.S. economy more than $9.8 billion annually.[1] As with most diseases, an earlier diagnosis typically leads to a better outcome and reduced healthcare costs. Although most men with prostate cancer are now being diagnosed earlier and with lower-stage disease, many patients progress into a more advanced stage where intensive therapy is often required.

For symptomatic metastatic castration-resistant prostate cancer (mCRPC), the standard of care has typically been chemotherapy with docetaxel. Docetaxel has been shown to offer modest improvements in overall survival compared to previous therapeutic options and helps to reduce the symptoms associated with metastatic disease.[2] However, docetaxel has not been shown to demonstrate consistent reductions in disease progression and is associated with toxic and unpleasant adverse events.[2]

For this reason, a major focus of oncology drug development has been improving the therapeutic treatment options available for mCRPC. The desired improvements include extending overall survival, limiting progression of the disease and associated symptoms, reducing the rate of medication adverse events, and improving patient quality-of-life. In the past three years, several pharmacologic products have been approved by the U.S. Food and Drug Administration (FDA) for use in mCRPC. Since approval of these new products, many oncologists have begun to question the clinical appropriateness of the current standards of care and the appropriate placement of the new therapies within the treatment paradigm of mCRPC. However, the true impact that these agents will have on the traditional treatment modalities for patients with advanced prostate cancer is largely unknown. Additionally, the potential use of these products in early-stage disease or in combination with other agents has yet to be evaluated, but questions have arisen regarding where these agents will ultimately fall within best-practice guidelines.

Recent Additions to the mCRPC Market

Moving away from the standard of chemotherapy, a great emphasis of drug development has been placed on identifying agents that can modify the mechanisms of tumor cell growth rather than general cellular division. In 2011, the first of a new generation of androgen synthesis inhibitors was

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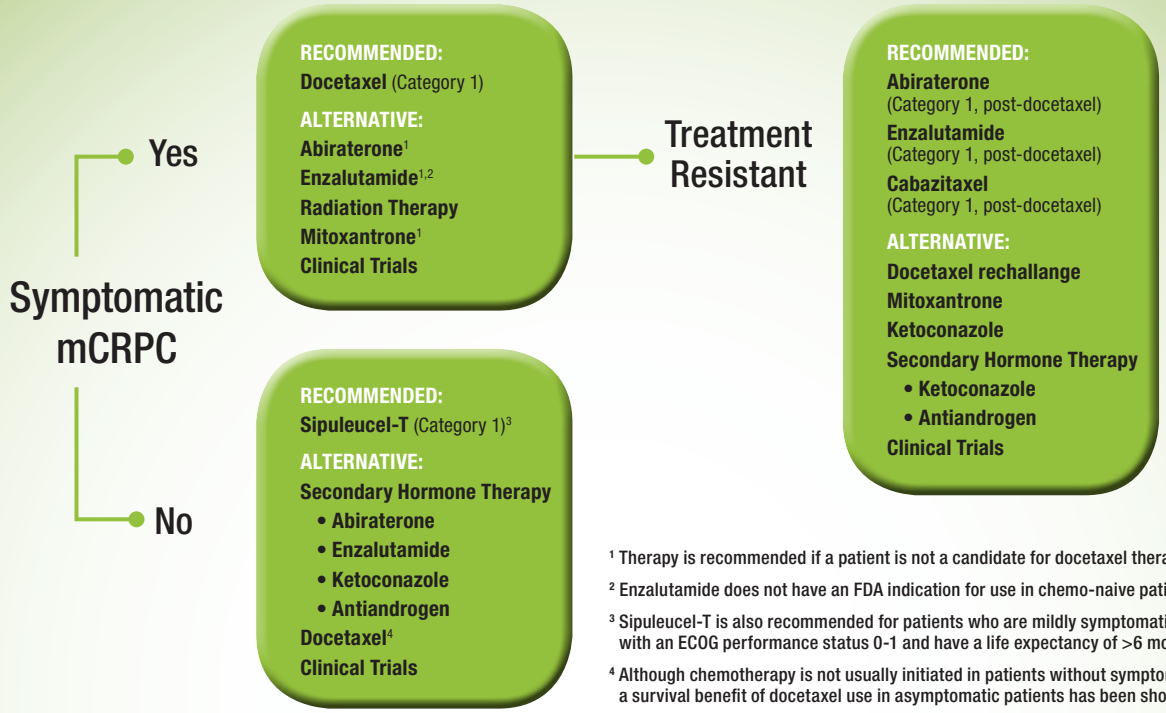
approved by the FDA, abiraterone (Zytiga, Janssen Biotech).[3] The initial indication approved by the FDA was for mCRPC in patients previously treated with docetaxel. Abiraterone is an irreversible inhibitor of CYP17A and blocks production of testosterone from nearly all sources.[4] The majority of androgen synthesis occurs in the testes and adrenal gland, but testosterone can be produced in small amounts from other locations as well. These small amounts, along with the up regulation of androgen receptors in prostate cancer cells, can lead to tumor cell growth. Abiraterone works by inhibiting androgen production from all of these locations and allows for a complete and total inhibition, reducing serum testosterone to undetectable levels. This androgen inhibition has resulted in overall survival improvements of 4.6 months compared to placebo (15.8 months vs. 11.2 months; $P<0.0001$).[5] In addition to the improved survival outcomes, abiraterone has a relatively mild side effect profile compared to chemotherapy. The most common side effects observed in clinical trials were edema, hypokalemia, and hypertension.[4] Another advantage compared to chemotherapy infusions is the availability of abiraterone as an oral tablet, which allows for a much easier dosing regimen and mitigates the need for administration by a healthcare provider.

One potential concern associated with abiraterone therapy is the need for concomitant prednisone. This is due to the abiraterone mechanism of action, which inherently decreases serum cortisol levels. The reduction in cortisol activates a negative feedback loop leading to an increased mineralcorticoid response. If left untreated, mineralocorticoid excess can cause hypokalemia, hypertension, and fluid overload—the primary adverse events associated with abiraterone therapy. This can be largely avoided by the addition of low-dose prednisione administered twice-daily.

In December 2012, the FDA expanded the abiraterone indication to allow for use in chemo-naïve patients.[6] This is perhaps the most pertinent therapeutic advancement for the treatment of mCRPC since docetaxel was approved for this indication in 2004. Oncologists now have a non-chemotherapy option for symptomatic patients with metastatic prostate cancer. There is strong evidence to support the abiraterone chemo-naïve indication demonstrating significant improvements in median survival compared to placebo (35.3 months vs. 30.1 months, respectively; $P=0.0151$).[7] Although it is difficult to conduct cross-trial comparisons, these results seem to surpass those demonstrated by docetaxel, sipuleucel-T (Provenge, Dendreon), or cabazitaxel (Jevtana, Sanofi-Aventis).[2,8,9] However, it is important to keep in mind when evaluating clinical trial results that docetaxel and cabazitaxel were compared to an active comparator rather than placebo. Regardless, this may provide the first stepping stone to eliminating the need for chemotherapy in the treatment of prostate cancer.

The most recent chemical entity approved for use in mCRPC is enzalutamide (Xtandi, Astellas Pharma).[10] Enzalutamide works through a variety of pathways to block the association of testosterone to the cellular androgen receptor.[11] The androgen receptor is found on prostate cancer cells and is considered the vehicle that drives tumor growth. Androgens, such as testosterone and dihydrotestosterone, activate the receptor and provide the fuel that powers tumor proliferation. Once the receptor is activated, the androgen receptor-complex translocates into the nucleus of the prostate cell, binds to DNA, and initiates transcription of androgen receptor-dependent genes required for cancer cell growth. Although direct androgen receptor activation is the primary mechanism for tumor growth, in many patients, the process can persist despite depletion of androgens to castration-like levels. Enzalutamide is able to block the androgen receptor with a binding affinity five times greater than bicalutamide (Casodex, AstraZeneca).[12] Enzalutamide also inhibits the translocation of the androgen receptor-complex to the nucleus and prevents DNA transcription of tumor growth genes, which is a clinical advantage over bicalutamide.[11] Its mechanism in these pathways is also significant because the androgen receptor can be activated by substrates other than testosterone. This can give it the ability to block receptor activation from other sources, if necessary. It also has resulted in significant improvements in overall survival compared to placebo (18.4 months vs. 13.6 months; $P<0.001$).[13] In clinical trials, enzalutamide has generated the most substantial improvements in overall survival compared to any of the other products indicated for post-docetaxel mCRPC. These were also the results from the interim analysis of the trials. An updated analysis is under way, which will provide a better understanding of the true survival benefits associated with enzalutamide therapy in patients who have previously failed docetaxel. Additionally,

NCCN Treatment Guidelines for Metastatic Castration-Resistant Prostate Cancer[16]



[1] Therapy is recommended if a patient is not a candidate for docetaxel therapy.

[2] Enzalutamide does not have an FDA indication for use in chemo-naive patients.

[3] Sipuleucel-T is also recommended for patients who are mildly symptomatic with an ECOG performance status 0-1 and have a life expectancy of >6 months.

[4] Although chemotherapy is not usually initiated in patients without symptoms, a survival benefit of docetaxel use in asymptomatic patients has been shown.

NCCN Guidelines have all therapies labeled as category 2A unless otherwise indicated. Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Generic name (trade name)	Disease state indication	Mechanism of action	Overall survival improvement over control (control)	Treatment Regimen	Duration of therapy	Cost
Docetaxel (Taxotere)	mCRPC	Microtubule stabilization	2.4 months (mitoxantrone)	75 mg/m^2 IV infusion every 3 weeks with prednisone 5 mg PO twice daily	10 cycles	$2,483/cycle
Abiraterone (Zytiga)	mCRPC	CYP17A Inhibitor	4.6 months (placebo)	1,000 mg PO daily with prednisone 5 mg PO twice daily	8 months	$5,819/month
Enzalutamide (Xtandi)	Chemotherapy-resistant mCRPC	Androgen receptor blocker	4.8 months (placebo)	160 mg PO daily	8 months	$7,450/month
Cabazitaxel (Jevtana)	Chemotherapy-resistant mCRPC	Microtubule stabilization	2.4 months (mitoxantrone)	25 mg/m^2 IV infusion every 3 weeks with prednisone 10 mg PO daily	6 cycles	$5,598/cycle
Sipuleucel-T (Provenge)	Asymptomatic (mildly symptomatic) mCRPC	Activated patient dendritic cells	4.1 months (placebo)	IV infusion every 2 weeks x 3 doses	3 treatments	$31,000/ treatment

Sources: 2, 4, 5, 8, 9, 11, 13 **Additional sources:** Taxotere [package insert]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2012. Jevtana [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2012. Sipuleucel-T [package insert]. Seattle, WA: Dendreon; 2011.

enzalutamide has shown improvements in quality-of-life parameters compared to placebo.[13] Enzalutamide provides these clinical advantages while offering a side effect profile much more tolerable than chemotherapy. The most prevalent side effects observed in clinical trials included fatigue, edema, hot flash, and headache.[11] Other benefits of enzalutamide include an oral formulation, ability to be taken with or without food, and no required liver function tests for monitoring.[11]

Pharmacoeconomic Considerations

Although the most important pharmacologic considerations made when reviewing oncology products should always be safety and efficacy, the influence these agents have on healthcare resources is always an area of concern. Managed care organizations (MCOs) are continually tasked with appropriately managing their financial resources and new pharmacologic agents are often associated with an increased cost burden. The primary goal is to provide access to the most therapeutically appropriate products that have the potential to improve overall outcomes, while simultaneously controlling the continually escalating healthcare expenditure. For many years, the pharmacoeconomic impact of oncology disease states was somewhat overlooked. However, with the addition of multiple market entrants, MCOs now have the ability to analyze potential opportunities for cost-savings in the oncology arena. Because of this, prostate cancer is receiving more managed care attention than in previous years. The products and regimens used to treat mCRPC are expensive, and MCOs need to assess whether or not newly approved pharmaceuticals will be cost-effective additions to their preferred medication formularies.

Docetaxel, the current first-line therapy for symptomatic mCRPC, may appear to be the least expensive of the current therapies at an initial glance, but that is without accounting for physician fees, infusion costs, or cost of managing adverse events.[12] Determining the true cost of therapy is difficult as these variables change greatly from patient to patient, depending on the infusion location (i.e., hospital outpatient infusions are generally more expensive than those performed in physician offices or infusion centers). Further complicating the financial analysis is the lack of sufficient real-world data evaluating the average length of time patients will be taking either abiraterone or enzalutamide. Both of these products are relatively new to the market and the data does not yet exist to accurately quantify treatment durations. However, it is expected that these new agents will be responsible for a greater degree of resource consumption compared with docetaxel.

In this class of pharmaceuticals, it will be important for MCOs to weigh both the clinical and financial risks and benefits of formulary management initiatives. Although docetaxel is the least expensive agent, it is also associated with a greater degree of adverse events and potentially reduced survival rates. The newer therapies may provide beneficial survival outcomes alongside a better side effect profile, but come at a higher cost when compared to chemotherapy. For mCRPC, it may be an appropriate strategy to analyze the financial burden based on the

NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) has developed guidelines for treating mCRPC.[16] The guidelines discuss first-line treatment options along with possible considerations if a patient is not eligible for a specific treatment. If a patient is symptomatic, the treatment becomes more aggressive and more options are considered to manage the associated symptoms, including skeletal-related events, and improve survival outcomes. Docetaxel is currently the recommended first-line treatment option for symptomatic mCRPC patients.[16] It is useful in extending survival outcomes and reducing the symptoms associated with mCRPC. After a trial of docetaxel therapy, there are several treatment options recommended by the NCCN. Both abiraterone and enzalutamide are currently listed as treatment options for patients who are not candidates for chemotherapy and are listed as first-line treatment options for post-docetaxel therapy.[16] Since abiraterone has recently been approved for use before docetaxel therapy in symptomatic mCRPC, it may receive a first-line consideration from the NCCN. For any patient who has progressed to metastasis, it is important to consider palliative care.

incremental cost of additional survival. This will help to evaluate the true cost-effectiveness of these agents. However, it may be too early to determine the real-world survival rates associated with the newly approved products.

Current Pharmacologic Sequencing and Potential for the Future

Following the approval of the new pharmacologic agents, therapeutic sequencing in mCRPC has been gaining more attention. In early stages of prostate cancer, oncologists typically inhibit the production of androgens with leuprolide (Lupron, Abbott Laboratories), a GnRH agonist, prior to blocking the androgen receptor with bicalutamide. It will be interesting to see if oncologists relay this treatment modality to mCRPC. As the mechanisms of action of the newly approved agents are similar to those of leuprolide and bicalutamide, will oncologists attempt to inhibit the production of androgens with abiraterone prior to blocking the receptor with enzalutamide? Where will docetaxel fit within the revised treatment paradigm? With the FDA approval for use in chemo-naïve mCRPC patients, abiraterone may be considered first-line therapy prior to docetaxel. If this becomes the preferred treatment option, what will oncologists use following abiraterone?

Post-Chemotherapy Survival Rates[5,9,13]

	Abiraterone plus prednisone N=797	Placebo plus prednisone N=398
Primary survival analysis		
Median survival (months)	14.8	10.9
P-value	<0.0001	
Hazard ratio	0.646	
Updated survival analysis		
Median survival (months)	15.8	11.2
Hazard ratio	0.74	

	Enzalutamide N=800	Placebo N=399
Median survival (months)	18.4	13.6
P-value	<0.0001	
Hazard ratio	0.63	

	Cabazitaxel plus prednisone N=378	Mitoxantrone plus prednisone N=377
Median survival (months)	15.1	12.7
P-value	<0.0001	
Hazard ratio	0.7	

Chemotherapy-Naïve Survival Rates[2,8,9]

	Docetaxel plus prednisone N=335	Mitoxantrone plus prednisone N=337
Median survival (months)	18.9	16.5
P-value	0.0094	
Hazard ratio	0.761	

	Abiraterone plus prednisone N=546	Placebo plus prednisone N=542
Median survival (months)	35.3	30.1
P-value	0.0151	
Hazard ratio	0.792	

	Sipuleucel-T N=341	Placebo N=171
Median survival (months)	25.8	21.7
P-value	0.032	
Hazard ratio	0.775	

Will docetaxel be the next agent in line or will other treatment options, like enzalutamide, be used instead?

Further complicating the sequencing process will be the results from ongoing clinical trials. Currently, there is a clinical trial under way with the goal of obtaining approval for enzalutamide to be used in chemo-naïve mCRPC patients.[14] The study is currently recruiting participants and will include patients who have mCRPC, have failed androgen deprivation therapy, and have not yet begun chemotherapy. This trial, as well as the abiraterone approval for use in chemo-naïve patients, may have a substantial impact on the current sequencing of agents in the treatment of mCRPC and may eliminate the need for chemotherapy in patients with prostate cancer.

Other clinical trials are evaluating the use of combination therapy to treat mCRPC. One specific trial is evaluating the safety and efficacy of co-administering abiraterone and enzalutamide.[15] Theoretically, these medications may have a synergistic effect due to their different mechanisms of action. The results of this study could be crucial in the future sequencing of mCRPC, but it is important to understand the possible risks and costs associated with such a combination. Would these combinations provide any benefits in overall survival or solely increase therapeutic toxicity? Another potential for combination therapy is sipuleucel-T and enzalutamide. Sipuleucel-T works on a unique pathway by enhancing an immune response to attack the tumor cells. Unlike other treatments, enzalutamide could be co-administered with sipuleucel-T since it does not require administration with prednisone. This combination could attack mCRPC through multiple pathways, potentially providing an improved response. However, this would also greatly increase the cost of care associated with treating mCRPC. Currently, combination therapy is not considered an appropriate treatment option for mCRPC and, until further studies prove otherwise, is not warranted.

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 the maximum health and survival benefits are obtained. With the approval of new pharmacologic agents, it is important to continually assess the current treatment modalities and determine when modifications should be made. Additional agents also highlight the need for a more structured management approach to ensure value in achieving positive outcomes. Moving forward, health plans will need to work with their network oncologists to develop treatment pathways that can reduce inappropriate resource utilization, optimize opportunities around palliative care, and provide access to clinically appropriate medications that can demonstrate meaningful overall survival, improve function, and enhance quality of life.

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Reevaluating the Pharmacoeconomic Implications of Antiretroviral Adherence in Patients with HIV Infection

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The advent of highly active antiretroviral therapy (HAART) has changed the treatment paradigm for human immunodeficiency virus (HIV) throughout the world. Effective antiretroviral therapy (ART) substantially reduces the morbidity associated with the infection, increases life expectancy, and helps prevent transmission.[1,2] Early HAART regimens used in the late 1990s were highly effective, but involved difficult combinations with large pill burdens, complex dosing schedules, and significant short-term side effects and long-term toxicity.[3] The approval of additional ART has improved treatment options for HIV-infected patients, who can now be treated effectively with simple, well-tolerated combinations. Since the first reports of acquired immunodeficiency syndrome (AIDS) in the United States,[4] the U.S. Food and Drug Administration (FDA) has approved more than 25 antiretroviral medications indicated to treat the infection.[2] These medications fall into six different categories based on their mechanism of action:

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors
- Integrase strand transfer inhibitors (INSTIs)
- CCR5 antagonists

In the United States, ART is now recommended for all HIV-infected patients, although the urgency of therapy is greatest for those with low CD4+ counts, a history of an AIDS-defining illness, HIV-associated nephropathy, HIV/hepatitis B virus coinfection, and pregnancy.[2] Currently, the preferred treatment for ART-naïve patients generally consists of two NRTIs in combination with an NNRTI, a PI (boosted with ritonavir), or an INSTI. The primary goals of ART are to prevent HIV-associated morbidity, prolong the duration and quality of life, restore and preserve immunologic function, suppress the HIV viral load, and prevent HIV transmission.[2]

Adherence to ART

Due to the substantial impact that suboptimal adherence can have on patients' overall health status, the federal government has begun an initiative to improve medication adherence within Medicare Advantage (MA) and Prescription Drug Plans (PDPs). Adherence to ART in patients with HIV/AIDS was added

as a display measure in the Centers for Medicare & Medicaid Services (CMS) Five-Star Quality Rating System. Health plans offering prescription coverage to Medicare beneficiaries are now being monitored on the rate of ART adherence within their patient populations. Although this is currently just a display measure, many MA plans and PDPs throughout the country are beginning to evaluate potential clinical programs to improve their rates of ART adherence in anticipation that this will become a contributing metric to their plan's overall Star Rating in the near future.[21]

There are multiple factors associated with nonadherence to ART. Some are at the patient level, such as mental illness, unstable housing, active substance abuse, low socioeconomic or education status, and major life crises.[2] Others are pharmacotherapy-specific, such as complex regimens, adverse drug reactions, and cost and insurance coverage issues. Interventions to improve adherence are as diverse as the multiple factors associated with nonadherence. Recommendations from the U.S. Department of Health and Human Services (HHS) include simplifying regimens, identifying potential barriers to adherence before starting therapy (e.g., active substance abuse), providing resources—such as pillboxes—to patients, and involving patients in ART regimen selection to allow for understanding of potential side effects and drug administration requirements.[2]

The guidelines provided by the HHS also highlight the need for individualizing ART.[2] This includes working closely with patients and agreeing on an understandable treatment plan that patients are comfortable with, giving them confidence in their ability to achieve success. Establishing a trusting relationship and maintaining strong communication will help improve medication adherence and positive outcomes over time.[2]

Although 100 percent adherence is the goal, the degree of adherence necessary for virologic suppression remains unclear. A study published in 2000 demonstrated that in patients receiving unboosted PI-based ART, ≥ 95 percent adherence was associated with significantly lower rates of virologic failure, higher CD4+ cell counts, and fewer days of hospitalization.[5] Aside from virologic failure, it is important to keep in mind that suboptimal adherence can lead to resistance and treatment failure, leaving fewer viable ART options.[6] More recent data suggests that ≥ 95 percent adherence may not be necessary to achieve viral suppression with contemporary ART regimens.[7] NNRTIs with longer half-lives, such as efavirenz, and ritonavir-boosted PI-based regimens make ART more forgiving of suboptimal adherence.[2]

The HHS currently recommends four preferred regimens for initial therapy in ART-naïve individuals.[2] Of these, one is available as a once-daily, single-pill regimen: efavirenz/emtricitabine/tenofovir (Atripla®), which was approved in 2006.[15] Unfortunately, none of these preferred regimens are available as generic products.

HHS-preferred initial combination regimens for ART-naïve patients[4]

Preferred Regimens	Level of Evidence*
Efavirenz/emtricitabine/tenofovir	A1
Ritonavir-boosted atazanavir + emtricitabine/tenofovir	A1
Ritonavir-boosted darunavir + emtricitabine/tenofovir	A1
Raltegravir + emtricitabine/tenofovir	A1
*A=strong; 1=data from randomized controlled trials	

Impact of Pill Burden on ART Adherence

Over the past two decades, a major focus of ART development has been to simplify the complex medication regimens associated with HIV treatment. Treatment of an infection that once required several different medications, multiple daily doses, and a high pill burden has become increasingly simplified with the approval of ART and coformulated products that allow simpler, more convenient dosing. Although it is generally accepted that reducing the frequency of administration results in positive improvements in medication adherence, the degree to which regimen simplification affects patient outcomes and healthcare-related expenditures remains a topic of debate.

The HIV-infected population is certainly not homogenous in terms of barriers to adherence. Therefore, it is important to explore the use of single-pill regimens in populations that might benefit from it the most. The potential adherence advantage of a single-pill regimen was explored in a prospective cohort study by Bangsberg and colleagues that included 118 participants who were homeless or marginally housed with a high prevalence (63 percent) of lifetime injection drug use.[8] Forty-seven participants were on a single-pill regimen (efavirenz/emtricitabine/tenofovir), 57 were on a PI-based regimen, and 14 were on an NNRTI-based regimen. Adherence was measured using unannounced pill counts. After controlling for confounders, including homelessness, injection drug use, depression, and prior ART use, the mean adherence remained significantly higher for the single-pill group compared with the mean adherence to all of the once-daily

regimens requiring greater than one pill (86 percent vs. 73 percent; p=0.001). Viral suppression (HIV RNA < 50 copies/mL) was also greater in the single-pill regimen group.[8]

The impact of switching to a single-pill, once-daily regimen was evaluated in a 48-week randomized controlled trial. Patients stable on ART with viral loads < 200 copies/mL for ≥ three months were stratified by prior NNRTI- or PI-based therapy and randomized to either efavirenz/emtricitabine/tenofovir or their baseline regimen.[9] Of the 300 patients who completed the study, both groups had non-inferior rates of maintaining viral loads < 50 copies/mL by time to loss of virologic response (TLOVR) analysis (single-pill regimen 87 percent; baseline regimen 85 percent). Switching did not appear to affect adherence, with self-reported adherence ≥ 96 percent for both groups. Discontinuation rates were similar for both groups; however, there were more discontinuations for treatment-emergent adverse events in the efavirenz/emtricitabine/tenofovir treatment arm compared with the baseline regimen group (5 percent vs. 1 percent).[9]

For many patients, it does not appear that there is a clear benefit to a single-pill, once-daily ART regimen over once-daily regimens requiring multiple pills. Larger, randomized controlled trials are needed to fully assess the benefit of single-pill regimens on adherence and virologic outcomes. The study by Bangsberg and colleagues does, however, provide support for using a single-pill regimen in patients with multiple barriers to adherence, highlighting the fact that ART selection must be highly individualized.

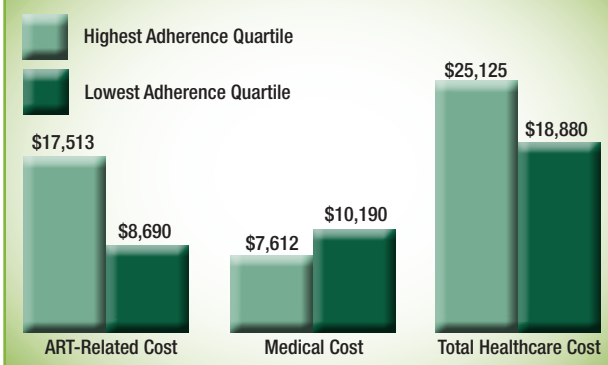
Pharmacoeconomic Implications of ART Adherence

With the advances in ART, HIV is considered a chronic, manageable condition, with patients having significantly greater life expectancies than when the virus emerged in the early 1980s. The remarkable clinical benefit of greater life expectancy has resulted in higher fiscal costs related to medical care. In 1992, the lifetime cost of treating HIV was estimated to be $119,300 based on a life expectancy of 6.8 years. Approximately 50 percent of these costs were for inpatient care.[10] In a 2006 study, the adjusted lifetime cost of HIV infection was estimated to be $385,200 based on a projected life expectancy of 24.2 years.[11] In contrast with the 1992 estimation, 73 percent of the medical costs were directly associated with ART.[11] As the treatment paradigm has evolved and as life expectancy has improved, minimizing the cost of ART while simultaneously improving sustained viral suppression is now the primary goal for HIV cost-containment strategies.

However, one important question remains: Does improved adherence decrease costs associated with ART? In a retrospective study by Gardner and colleagues, better adherence was associated with lower healthcare utilization but higher total medical costs.[12] However, in a sensitivity analysis that used the one-year costs of first-line generic ARTs available in low- and middle-income countries, results showed that improved adherence reduces total medical costs.[12] This analysis alludes to the potential impact that future generic ARTs may have on the U.S. marketplace.

In the meantime, separating the pharmacologic components of expensive combination products into individual prescriptions may be a cost-effective treatment option for patients without significant barriers to adherence. A major opportunity for this will arise once efavirenz becomes generically available in the near future.[13] The potential to combine generic efavirenz, generic lamivudine, and brand Viread® (tenofovir) may provide a cost-savings opportunity for health plans when compared to Atripla® therapy. However, this will be associated with an increased pill burden; plans will have to determine if the financial savings are worth the potential for reduced medication adherence. Additionally, replacing emtricitabine (one of the three components in Atripla®) with lamivudine may diminish the potency as a first-line regimen and lead to a greater likelihood of viral resistance.[14] Insurance providers hoping to use this strategy to generate savings will have to ensure that their patients with HIV receive adequate support to improve medication adherence and increase their likelihood of achieving viral suppression.

Annual Healthcare Cost Associated with ART Adherence in Patients with HIV[12]



Considerations for Managed Care

With generic ART options on the horizon, further pharmacoeconomic analyses will have to be conducted to determine the true cost-effectiveness of these agents compared

Costs of ART Single-Pill Regimens[15-20]

Brand Name	Components	Manufacturer	WAC/Month	AWP/Month
Atripla®	efavirenz/emtricitabine/tenofovir	Bristol-Myers Squibb; Gilead Sciences	$1,878.23	$2,253.88
Complera®	rilpivirine/emtricitabine/tenofovir	Gilead Sciences	$1,936.53	$2,323.84
Stribild®	elvitegravir/cobicistat/emtricitabine/tenofovir	Gilead Sciences	$2,342.40	$2,811.00
WAC=wholesale acquisition cost; AWP=average wholesale price				

with branded products. Until this time, managed care organizations need to consider the potential advantages offered by single-pill regimens and determine whether the modest improvement in medication adherence is worth the additional pharmacy expenditure and impact on outcomes.

One consideration that has not been accounted for in adherence-based trials is the impact on viral resistance. It is largely unknown how improvements in adherence, specifically modest improvements, influence viral resistance over the long term. This is becoming a greater point of concern as the life expectancy of patients with HIV is being extended. It has been a difficult outcome to quantify, as most clinical studies evaluating adherence are relatively short in duration. Decreasing the risk of viral resistance may be a long-term benefit of single-pill regimens. As there is not a firm understanding of the reduction in viral resistance associated with improving adherence, the economic implications remain unclear. However, if the single-pill regimens are associated with improvements in long-term viral suppression and reduced resistance via improved adherence, these outcomes may be enough to justify a higher up-front medication cost.

Regardless of the financial implications, adherence is necessary for optimal outcomes. Additionally, the potential incorporation of the HIV adherence display metric into the overall Star Rating measurement calculation will increase the need for managed care organizations to improve medication adherence within this category. Ensuring medication adherence in patients with HIV has been a formidable challenge in previous decades, and even with the development of simplified therapeutic regimens, it will remain a challenge for many patients. A comprehensive approach to improving adherence will provide the opportunity to improve care coordination.

Special thanks to Joel E. Gallant, MD, MPH, and David R. Bangsberg, MD, MPH, for their contributions to this article, and to Matthew L. Romo, PharmD, for providing editorial support.

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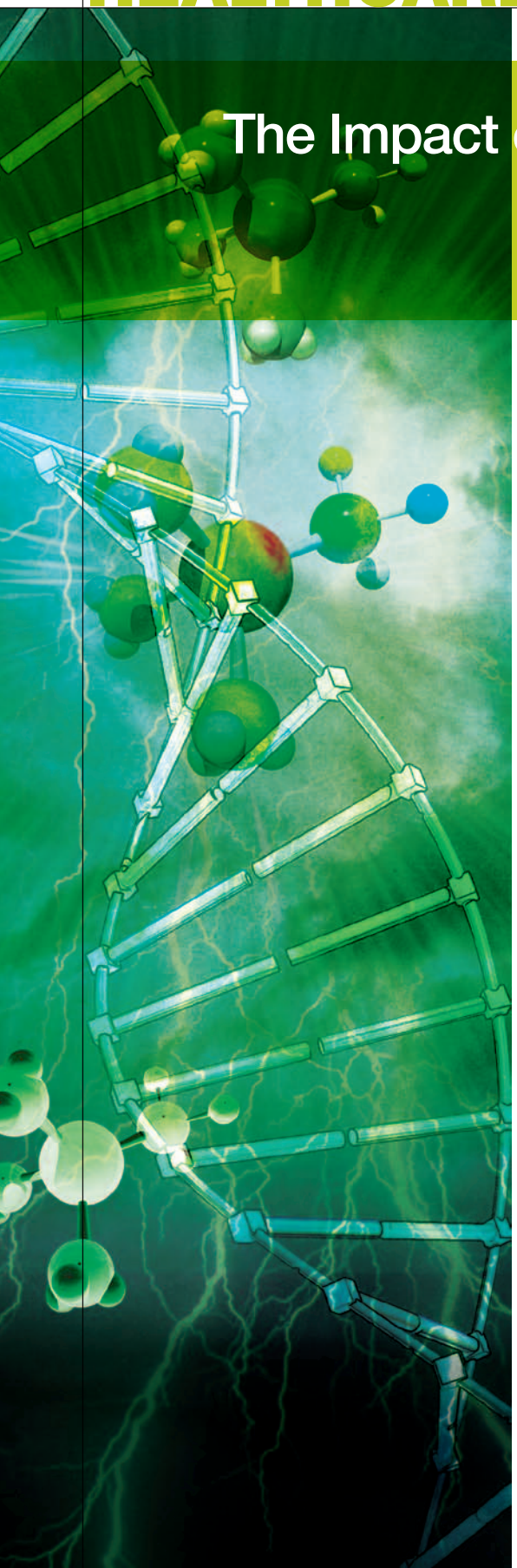


The Impact of Health Insurance Exchanges on Managed Care

Christine Welniak

The re-election of President Barack Obama set the stage for the continued rollout of the Patient Protection and Affordable Care Act (PPACA), including the advent of government-regulated health insurance exchanges (HIExs). Along with increases in Medicaid eligibility, government-run HIExs are the means to expand the number of insured Americans, and private payors could see an influx of 25 million new enrollees over the next 10 years.[1] However, the PPACA limits the insurers' ability to balance the price of premiums with the risk of covering a given patient population. It also mandates that "essential health benefits" be included in most plans available on HIExs. While these stipulations and others included in the PPACA may make it challenging for insurers to realize profits on HIEx plans, it is possible that over time, some Medicare or Medicaid patients could move to HIExs. Thus, insurers who make early efforts to optimize their plans and operations to fit the new, public HIEx paradigm could be well-positioned to profitably compete for more than 50 million covered lives.

HIExs: Clearinghouses vs. Active Purchasers

The majority of HIExs—including those managed by the federal government—will function as clearinghouses for all qualified health plans (QHPs) that apply to participate on the HIExs. States that wish to administer their own HIExs had to file their plans with the U.S. Department of Health and Human Services (HHS) in December 2012. Only 18 states and the District of Columbia opted to implement their own HIExs, with seven states choosing a state-federal partnership at that time. The remaining states had until February 15, 2013, to indicate whether they would pursue a state-federal partnership or opt for the federal government to implement and oversee HIExs on their behalf. All HIExs are required to be ready to offer open enrollment by October 2013, with coverage beginning on January 1, 2014.[2]

Although the PPACA sets certain requirements that will apply to all plans offered on all exchanges (discussed later in this article), QHPs offered on HIExs will depend on the selection parameters set by the states and/or the federal government. To begin with, each state must select a health plan, based on an existing small group, commercial HMO, state employee, or federal employee program, that will serve as the benchmark for selecting QHPs to be offered on the exchanges. If states do not select a benchmark plan, HHS will select a benchmark on their behalf.[3]

In the clearinghouse model, HHS presumes that consumer choice will foster competition on both quality and price.[4] However, many industry

observers expect price to be the primary dynamic on exchanges. "HIExs will lead to the commoditization of insurance products," said David Brailer, MD, PhD, CEO of Health Evolution Partners, a healthcare private equity firm. "The available plans will move toward the lower-priced options. There won't be a lot of so-called Cadillac or premium plans. Most people will want to have something that is basic, so I think we'll see a proliferation of low-cost plans."

The PPACA lists four levels of coverage based on their actuarial value that may generally be offered by insurance providers. The plan's actuarial value is based on the average percentage of total covered healthcare costs paid for by the plan. These levels are:

- **Bronze: 60%**
- **Silver: 70%**
- **Gold: 80%**
- **Platinum: 90%[6]**

Others concur. "Insurers may have very little flexibility on how they set up the plans for HIExs," said Avik Roy, a senior fellow at the Manhattan Institute for Policy Research. "If you standardize the product and make it more uniform, it makes it easier for consumers to choose. But if Aetna, United Healthcare, and other insurers—including regional plans—can't compete on the most efficient plan design, that means they have to compete on price."

It is possible that factors other than price will influence QHPs offered on state-run HIExs. As of November 2012, six states (California, Connecticut, Massachusetts, Oregon, Rhode Island, and Vermont) as well as the District of Columbia had indicated that they would be active purchasers of QHPs on their HIExs. Active purchasers can set criteria, such as the plan's quality or coordination of care, beyond those set forth by the state benchmark plan.[5]

Economist Gail Wilensky, PhD, senior fellow at Project HOPE, an international foundation dedicated to health education and humanitarian assistance, said, "How insurance companies fare, and what experiences they have, will depend very much on how the exchanges are set up and whether the organizers of the exchanges attempt to use their purchasing power. If states use too much pressure to exchange volume for price, they could essentially be creating Medicaid-type plans. That could be a problem with consumers and small businesses. If plan offerings look like Medicaid, I think employees will shy away from HIExs. If states opt to offer plans that have good value and if most employees will receive subsidies in the HIEx, it could be to the benefit of employees and insurers for employees to get their insurance in the HIEx. Time will tell."

Essential Benefits

The PPACA specifies that QHPs in each state offer 10 "essential health benefits," shown in Figure 1, which are supposed to be "equal in scope" to those offered by employer-sponsored insurance (ESI). In addition to offering subsidies to low- and moderate-income families and individuals, the PPACA provides some flexibility as to consumers' financial commitments to health insurance. Specifically, it delineates four classifications (platinum, gold, silver, and bronze) to indicate the QHPs' estimated level of contribution to overall healthcare benefits. As shown in Figure 1, these metal classifications equate to the level of expected spending on the part of insurer and consumer. For instance, gold plans have an actuarial value (AV) of 80

Fig. 1 **Essential Benefits and Cost-Sharing Levels[6]**

Obama's Pay for Performance

The Obama Administration is effecting change through the Centers for Medicare & Medicaid Services (CMS), which has introduced several well-publicized, pay-for-performance models, including penalties for 30-day hospital readmissions for heart failure, pneumonia, or heart attack and the introduction of Accountable Care Organizations (ACOs). ACOs are responsible for a patient's total healthcare utilization. Despite the risk of being accountable for services used outside the ACOs' domain, interest in this model has exploded. Oliver Wyman Group, a management consulting firm, estimates that 500 providers submitted ACO applications in the fall of 2012, a substantial increase from the 32 Pioneer ACOs named in December 2011 and the addition of 116 ACOs through July 2012.[17]

CMS' Bundled Payments for Care Improvement initiative, a pilot program that became effective in January 2013, is another effort to provide incentives to reduce healthcare costs. The Bundled Payments initiative has four models in which providers can participate:

- Model 1: Retrospective Acute-Care Hospital Stay Only
- Model 2: Retrospective Acute-Care Hospital Stay Plus Post-Acute Care
- Model 3: Retrospective Post-Acute Care Only
- Model 4: Prospective Acute-Care Hospital Stay Only[18]

Models 1 to 3 will not use a bundled payment for care. Rather, CMS will set a target payment based on a discount to the historical amount paid to the organization for a specific type of service. Hospitals that opt for Model 2 could face challenges, as data suggest that 90-day post-discharge care can approximate or surpass the cost of the initial hospitalization.[19]

Model 4 represents a greater departure from established Medicare payment mechanisms, and will comprise bundled payments, with a minimum discount of 3 percent to MS-DRG reimbursement to hospitals for certain services. In addition, hospitals that participate in Model 4 will be responsible for paying for physician and other services from the bundled payment.[20]

percent, meaning that the insurer will pay for 80 percent of the benefits covered by the plan and the consumer will cover 20 percent of the costs.[6]

While small businesses with fewer than 25 full-time employees may find HIExs to be an attractive method to fulfill their PPACA-mandated obligation of providing health insurance to employees, purchasers of individual plans may face sticker shock, given the political rhetoric that the PPACA would ensure "affordable" healthcare. An analysis of ESI plans tracked by the Kaiser Family Foundation's Health Research and Educational Trust 2010 Employer Health Benefit Survey as well as plans sold in the individual insurance market in 10 states revealed the dichotomy between ESI and individual market plans. Researchers found that 80 to 89 percent of ESI plans met the qualifications to be considered a gold health plan, whereas only 2 percent of plans purchased in the individual market met this criteria. Furthermore, more than half of non-ESI plans were below the threshold for even a bronze plan. This suggests that premiums for non-group policies sold on HIExs will need to increase in order to cover the essential health benefits and AV standards set forth in the PPACA.[7] Indeed, some industry participants believe premiums could increase 20 to 50 percent, with some segments rising as much as 100 percent.[8]

Premium Restrictions

While premiums in the individual market will likely need to increase to merit bronze plan criteria, the PPACA limits the insurers' ability to balance the risk of a patient population with the monthly premium charged. Premiums may vary based only on differences in geography, age, number of beneficiaries (i.e., individual vs. family), and tobacco use. Premiums may not vary based on whether a patient is deemed high risk or has a pre-existing condition.[9] In addition, the PPACA limits deductibles in the small group market to $2,000 for individuals and $4,000 for families.[10] Total out-of-pocket expenses for low- and moderate-income families and individuals are also limited and vary based on the income relative to the federal poverty level (FPL). For instance, total out-of-pocket expenses for an individual with an income of 200 to 300 percent of the FPL are capped at $2,975.[11]

These restrictions may make it difficult for insurers to establish premiums, deductibles, and out-of-pocket expenses that adequately cover costs associated with covered health benefits. This conundrum is magnified by two factors: 1) uncertainty related to how states will define risk pools, and 2) the profile of first-time insured individuals. The PPACA

permits states to choose to either aggregate small group and individual insurance plans into one risk pool or segment them into two separate pools.[9] PricewaterhouseCoopers' Health Insurance Institute estimates that most of the newly insured will be relatively young individuals in good health,[12] which presumably would balance the risk if a state were to combine the small group and individual markets.

However, states that have performed their own analyses have arrived at different conclusions on the impact on rates if the small group and individual are put into one risk pool, which may reflect each state's demographics and assumptions regarding the newly insured. For instance, an analysis of combining the risk pool in New Jersey suggested that premiums for small groups would not increase, whereas those for individuals would. Comparatively, an analysis performed by the United Hospital Fund of New York calculated that premiums for individual insurance would decrease 13 to 41 percent if a single risk pool were used.[13]

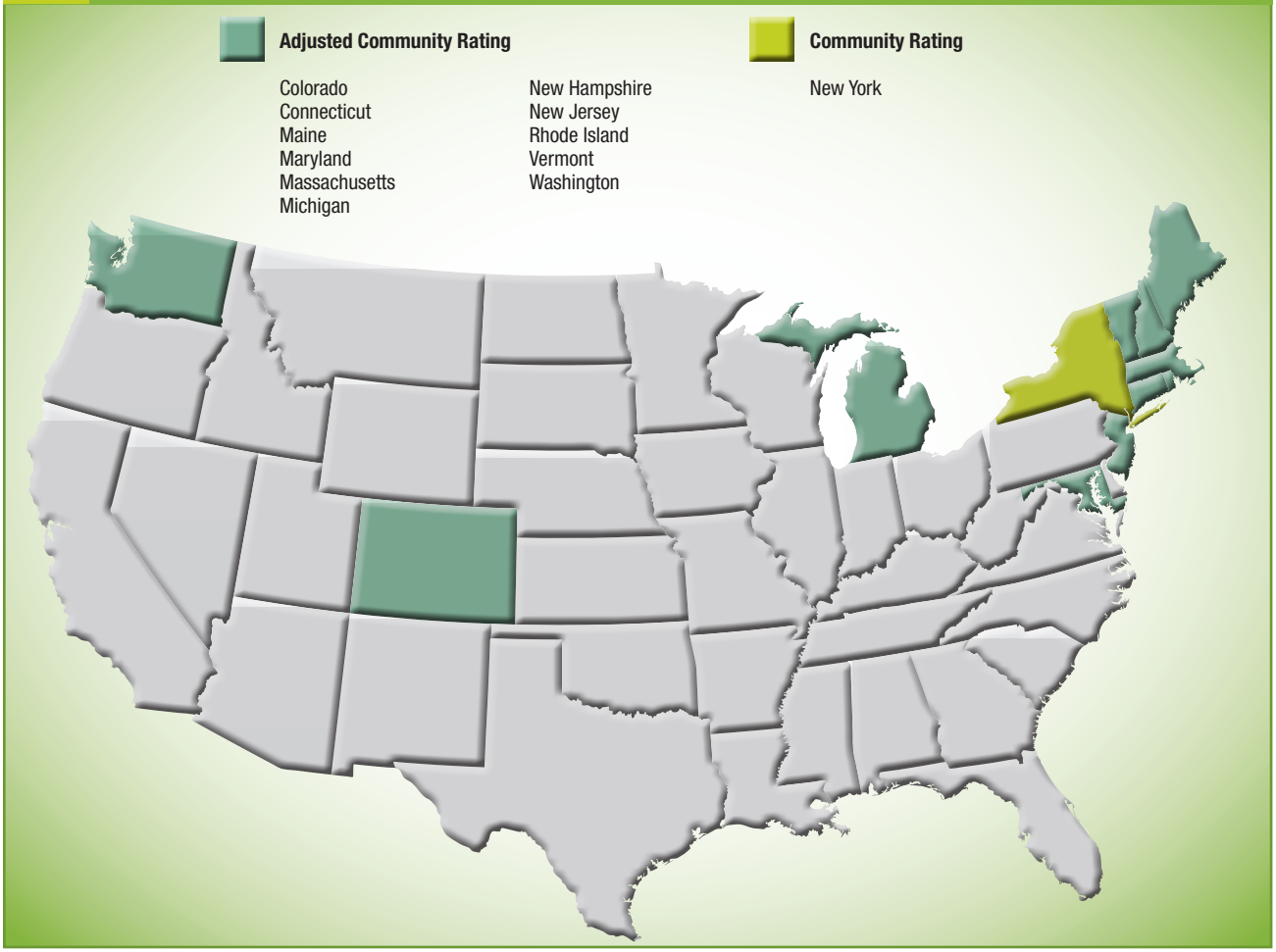
States that already had some type of community-rating requirement for health insurance (prior to enactment of the PPACA) will likely experience less disruption with HIExs. New York is the only state with a community rating restriction, which does not permit variance in premiums based on age, health status, gender, or lifestyle considerations for small-group insurance.[14,15] As shown in Figure 2, there are 11 states that use adjusted community ratings, which allow for some variation on premiums, in small-group insurance.[15]

What Can Insurers Do?

PricewaterhouseCoopers' Health Insurance Institute estimates HIExs could represent a $205 billion opportunity by 2021.[12] Insurers can take several steps to prepare for entry into the large HIEx market, including:

Fig. 2

States with Community or Adjusted Community Ratings for Small Groups[15]



Glossary

ACO: Accountable Care Organization, a payment and care model developed by Medicare. Providers that are designated as ACOs by Medicare are responsible for all healthcare expenses of Medicare beneficiaries in their purview and are required to meet certain performance measures, after which they can share in any cost-savings they are able to demonstrate.

AV: Actuarial value, the percentage of total healthcare costs that will be borne by the insurer

CMS: Centers for Medicare & Medicaid Services

Community rating: Signifies that the premium for a given health insurance policy will not vary based on age, gender, health status, or other factors

ESI: Employer-sponsored insurance

Essential health benefits: The Patient Protection and Affordable Care Act delineates 10 benefits that all plans offered on health insurance exchanges must cover.

FPL: Federal poverty level

HHS: U.S. Department of Health and Human Services

HIExs: Health insurance exchanges, from which individuals and small companies can purchase health insurance. Privately run HIExs have been in use for many years. The Patient Protection and Affordable Care Act mandated the creation of government-run exchanges, which are slated to begin open enrollment in October 2013, with coverage for plans purchased on the exchanges to be effective on January 1, 2014.

PPACA: Patient Protection and Affordable Care Act, enacted in 2010

QHP: Qualified health plan. In order for health plans to be offered on any health insurance exchange, the plans must meet criteria selected by each state or the federal government.

- **Evaluate HIEx size and dynamics.** Factors to consider include the number of potential enrollees in a given state, whether the HIEx will be operated by the state or the federal government, and the variance between pre-PPACA state insurance premium review and statutes in the PPACA. Approximately 40 percent of HIEx enrollees are expected to come from California, Texas, Florida, New York, and Illinois, according to some estimates.[12] A clearinghouse model, such as that planned by the federal government, may facilitate entry into HIExs for many insurers, as all QHPs will be offered.[4] However, insurers will need to evaluate the risk-adjustment methodology of each HIEx in order to ensure that premiums can be adjusted to account for the risk of the covered beneficiaries. At this time, little is known about which methodologies will be employed by the federal and state governments.[16]
- **Reduce costs and inefficiencies.** The PPACA and advent of HIExs will likely heighten payors' focus on eliminating redundancies within a given healthcare system. "Insurers that do well on HIExs will really be the most clever about costs and cost containment," Roy said. "They'll have to steer people to the lowest-cost doctors and hospitals or develop algorithms on where patients should go to be treated, which would improve quality but lower the cost. They'll need to clamp down on wasteful or unnecessary tests."
- **Partner with quality providers.** Analysis of overall healthcare costs by provider is also critical, as physicians and facilities that accept lower payments from insurers may not be less expensive in the long run. "Insurers will have to look at which providers provide better care at lower costs," Dr. Brailer said. "Often bad providers are the most expensive. The way for insurers to survive is to choose their partners carefully. It's possible to build a low-cost network of high-quality providers. Insurers who do that will be the winners in this environment."
- **Demonstrate value.** For insurers with a presence in states that will be active purchasers in their own HIExs, preparing metrics that prove the insurer's value could be a winning proposition. "Value takes into account what you get and what it costs you, so it's not just the lowest price. Insurers will have to demonstrate better value in terms of credible, empirical data that shows that high-value providers make a difference in terms of keeping employees well or helping them recover quicker and more efficiently. If insurers can do this, they may be rewarded by purchasers who understand the difference between lowest price and best value," Dr. Wilensky said.

> **"Value takes into account what you get and what it costs you, so it's not just the lowest price. Insurers will have to demonstrate better value in terms of credible, empirical data that shows that high-value providers make a difference in terms of keeping employees well or helping them recover quicker and more efficiently."**
>
> –Gail Wilensky, PhD, senior fellow at Project HOPE

States and the federal government have much to do before open enrollment in HIExs begins in October. Interestingly, the level of public interest in using HIExs is unclear. "There's a profound unknown with HIExs," Dr. Brailer said. "We don't know if we'll see 3 million or 90 million individuals interested in purchasing insurance through a HIEx. It's rare that you see a public policy rolled out with such little testing. We've gone from theory to practice at a national level without having the experience at the state level."

Way of the Future?

Still, HIExs have moved beyond political debate to the realm of implementation. Once in place, they will likely be difficult to dismantle. Some industry observers do not see this necessarily as a negative. Roy, who was a healthcare adviser to presidential candidate Mitt Romney, sees HIExs as a way to reduce government spending on healthcare. "The cost of caring for individuals on the exchanges will probably be lower than the cost of Medicare, so some Medicare patients could be migrated to the exchanges. You could also migrate Medicaid patients to the exchanges. If you think about it, over the next 10, 20, 30 years, what do we do about the government spending too much money on healthcare? This may be how you do it."

If Roy is correct, insurers may be well-served by optimizing their offerings, operations, and provider affiliations in order to capitalize on this nascent opportunity.

Special thanks to John Fox, MD, MHA, Senior Medical Director, Priority Health, for his contribution to this article.

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PIPELINE TRENDS

NEW DRUG APPROVALS

Drug	Manufacturer	Approval Date	Indication
Stribild™ (cobicistat, elvitegravir, emtricitabine, and tenofovir)	Gilead	August 27, 2012	Combination antiretroviral tablet for treatment of HIV-1 infected, treatment-naïve adults
Linzess® (linaclotide)	Forest Labs	August 30, 2012	Guanylate cyclase-c agonist capsule for treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults
Xtandi® (enzalutamide)	Astellas	August 31, 2012	Androgen receptor inhibitor capsule for the treatment of metastatic castrate-resistant prostate cancer
Bosulif™ (bosutinib)	Pfizer	September 4, 2012	Kinase inhibitor tablet for treatment of adults with chronic myelogenous leukemia
Aubagio® (teriflunomide)	Sanofi-Aventis	September 12, 2012	Pyrimidine synthesis inhibitor tablet for treatment of patients with relapsing forms of multiple sclerosis
Stivarga® (regorafenib)	Bayer	September 27, 2012	Kinase inhibitor tablet for treatment of metastatic colorectal cancer
Fycompa® (perampanel)	Eisai	October 22, 2012	AMPA glutamate receptor agonist tablet indicated for adjunctive therapy for treatment of partial-onset seizures in patients with epilepsy 12 years and older
Synribo™ (omacetaxine mepesuccinate)	Teva	October 26, 2012	Protein synthesis inhibitor injection for treatment of adult patients with chronic myeloid leukemia (CML)
Xeljanz® (tofacitinib)	Pfizer	November 6, 2012	Janus kinase inhibitor tablet for treatment of adults with moderately to severely active rheumatoid arthritis
Cometriq™ (cabozantinib)	Exelixis	November 29, 2012	Kinase inhibitor capsule for treatment of progressive, metastatic medullary thyroid cancer
Iclusig™ (ponatinib)	Ariad	December 14, 2012	Kinase inhibitor tablet for treatment of chronic myeloid leukemia (CML) and philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)
Signifor® (pasireotide)	Novartis	December 14, 2012	Somatostatin analog injection for treatment of patients with Cushing's disease
Bivigam™ (human immune globulin)	Biotest	December 21, 2012	Immune globulin infusion indicated for treatment of primary humoral immunodeficiency
Gattex® (teduglutide)	NPS	December 21, 2012	Glucagon-like peptide 2 injection for treatment of adults with short-bowel syndrome
Juxtapid™ (lomitapide)	Aegerion	December 21, 2012	Microsomal triglyceride transfer protein inhibitor capsule indicated to reduce low-density lipoprotein, total cholesterol, apolipoprotein B and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia
Eliquis® (apixaban)	Bristol-Myers Squibb	December 28, 2012	Factor Xa inhibitor anticoagulant tablet indicated to reduce risk of stroke and dangerous blood clots in patients with atrial fibrillation not caused by a heart valve problem
Sirturo™ (bedaquiline)	Janssen	December 28, 2012	Diarylquinoline antimycobacterial tablet used as part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis
Fulyzaq™ (crofelemer)	Salix	December 31, 2012	Anti-diarrheal tablet for relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy
Nesina® (alogliptin)	Takeda	January 25, 2013	Dipeptidyl peptidase-4 inhibitor tablet for treatment of type 2 diabetes
Oseni® (alogliptin/pioglitazone)	Takeda	January 25, 2013	Dipeptidyl peptidase-4 inhibitor and thiazolidinedione fixed-dose combination tablet for the treatment of type 2 diabetes
Kazano® (alogliptin/metformin)	Takeda	January 25, 2013	Dipeptidyl peptidase-4 inhibitor and biguanide antihyperglycemic fixed-dose combination tablet for the treatment of type 2 diabetes
Kynamro™ (mipomersen)	Genzyme/Isis	January 29, 2013	Oligonucleotide inhibitor of apolipoprotein B-100 synthesis injection indicated for the treatment of patients with homozygous familial hypercholesterolemia

NEW FDA-APPROVED INDICATIONS

Drug Name	Approved	New Indication
Nucynta® (tapentadol)	August 28, 2012	Approved for management of neuropathic pain associated with diabetic peripheral neuropathy
Afinitor® (everolimus)	August 29, 2012	Approved to treat a rare brain tumor subependymal giant cell astrocytoma (SEGA)
Exelon® (rivastigmine)	August 31, 2012	Higher dose approved for treatment of mild to moderate Alzheimer's disease
Prolia® (denosumab)	September 21, 2012	Treatment of bone loss in men with osteoporosis
Humira® (adalimumab)	September 28, 2012	Approved for treatment of ulcerative colitis
Abraxane® (paclitaxel)	October 11, 2012	Approved for first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)
Rituxan® (rituximab)	October 19, 2012	Approval for use of a 90-minute infusion for previously untreated follicular non-Hodgkin's lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL) patients
Xarelto® (rivaroxaban)	November 2, 2012	Approved to treat and reduce recurrence of blood clots
Promacta® (eltrombopag)	November 16, 2012	Approved for thrombocytopenia in patients with chronic Hepatitis C
Zytiga® (abiraterone)	December 10, 2012	Approved to treat late-stage castration-resistant prostate cancer before chemotherapy
Kineret® (anakinra)	December 21, 2012	Approved for treatment of children and adults with neonatal-onset multisystem inflammatory disease (NOMID)

Disclosures: The information contained in Pipeline Trends is current as of January 2013. Estimated dates are subject to change according to additional indication/approvals, patents, patent litigation, etc. Information available from **www.fda.gov.**

NEW FORMULATIONS AND DOSAGE FORMS

Drug Name	Manufacturer	Approved	Advertised Advantage
Adasuve® (loxapine)	Alexza	December 21, 2012	Inhalation powder indicated for the acute treatment of agitation associated with schizophrenia or bipolar disorder in adults
Bethkis® (tobramycin)	Cornerstone	October 12, 2012	A 300 mg/4 mL inhalation solution for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Nucynta® (tapentadol)	Janssen	October 15, 2012	A 20 mg/mL oral solution for the management of moderate to severe acute pain in adults
Oxtellar XR™ (oxcarbazepine)	Supernus	October 19, 2012	Extended-release tablet formulation of oxcarbazepine for the adjunctive therapy of partial seizures
Skyla® (levonorgestrel)	Bayer	January 9, 2013	Intrauterine system (IUS) indicated for prevention of pregnancy for up to three years
Uceris® (budesonide)	Santarus	January 14, 2013	Extended-release tablet indicated for the induction of remission in patients with active, mild-to-moderate ulcerative colitis
Zecuity™ (sumatriptan)	NuPathe	January 17, 2013	Transdermal patch indicated for the acute treatment of migraine

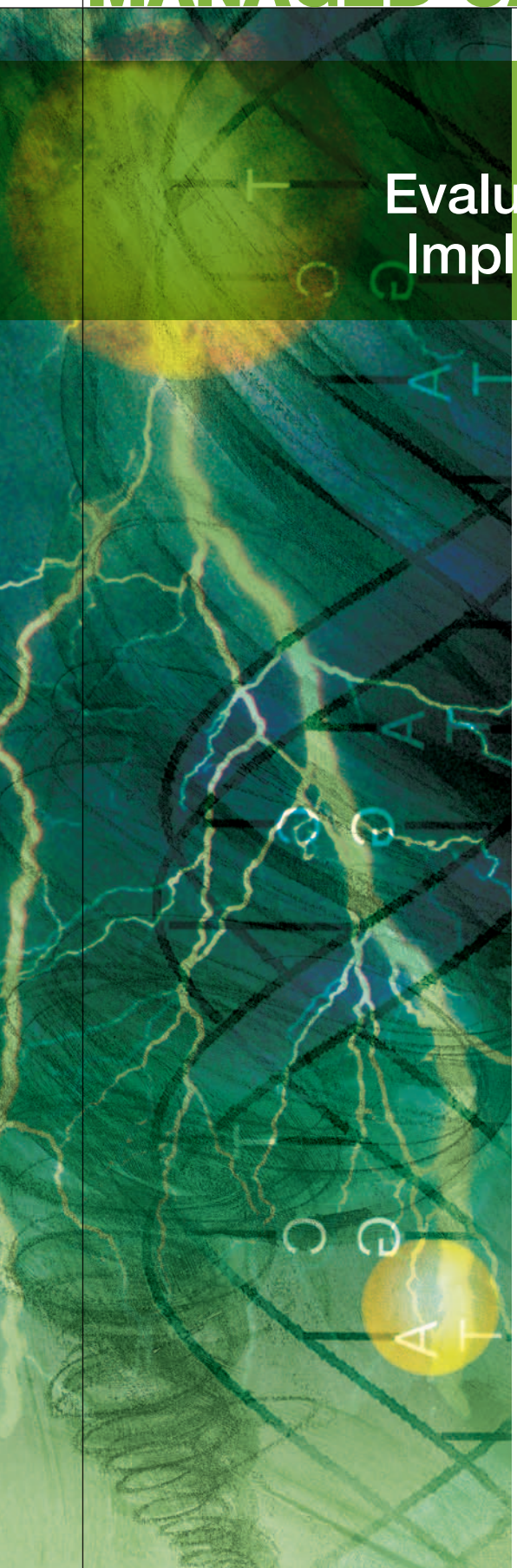
NEW FIRST-TIME GENERIC DRUG APPROVALS

Drug Name	Date
Guanfacine HCl (Intuniv®)	Approved: October 5, 2012
Trospium chloride (Sanctura XR®)	Approved: October 12, 2012
Nepafenac (Nevanac®)	Approved: October 16, 2012
Sildenafil (Revatio®)	Approved: November 6, 2012
Fenofibrate (Tricor®)	Approved: November 20, 2012
Betamethasone (Luxiq®)	Approved: November 26, 2012
Candesartan/HCT (Atacand HCT®)	Approved: December 4, 2012
Griseofulvin (Grifulvin V®)	Approved: December 14, 2012
Lamotrigine extended-release (Lamictal XR®)	Approved: December 26, 2012
Phenytoin chewable tablet (Dilantin®)	Approved: December 26, 2012
Tranexamic acid (Lysteda®)	Approved: December 27, 2012
Rizatriptan (Maxalt®)	Approved: December 31, 2012
Rizatriptan disintegrating tablet (Maxalt-MLT®)	Approved: December 31, 2012
Finasteride (Propecia®)	Approved: January 2, 2013
Finasteride (Propecia®)	Approved: January 2, 2013
Oxymorphone HCl ER (Opana ER®)*	Launched: January 4, 2013
Pioglitazone HCl/Glimepiride (Duetact®)	Approved: January 4, 2013
Betamethasone/Calcipotriene (Taclonex®)	Approved: January 14, 2013

**Not AB-rated to tamper-resistant formulation of Opana ER.*

PROJECTED FIRST-TIME GENERIC ENTRY

Drug Name	Date
Zomig® (zolmitriptan)	May 2013
Zomig-ZMT® (zolmitriptan)	May 2013
Aciphex® (rabeprazole)	May 2013
Rilutek® (riluzole)	June 2013
Asacol® (mesalamine)	June 2013
Temodar® (temozolomide)	August 2013
Advicor® (niacin/lovastatin)	September 2013
Niaspan® (niacin extended release)	September 2013
Exalgo® (hydromorphone HCL)	November 2013
Cymbalta® (duloxetine)	December 2013
Vanos® (fluocinonide)	December 2013
Vivelle-Dot® (estradiol transdermal patch)	December 2013



Hepatitis C Virus: Evaluating the Clinical and Financial Implications of Triple-Drug Therapy

Hepatitis C virus (HCV) is the most prevalent blood-borne pathogen in the United States, with approximately 3.2 million Americans chronically infected.[1] From a managed care perspective, HCV has always been a costly condition to treat. In 2011, the expense of treating HCV patients increased dramatically after the U.S. Food and Drug Administration (FDA) approval of two new protease inhibitors (PIs), boceprevir (Victrelis; Merck & Co, Inc.) and telaprevir (Incivek; Vertex Pharmaceuticals).[2,3] Following the approval of these agents, the American Association for the Study of Liver Diseases (AASLD) updated its clinical practice guidelines to recommend the use of triple-drug therapy in patients with genotype 1 HCV: one of the new direct-acting protease inhibitors in combination with standard pegylated interferon-alpha and ribavirin (peg-IFN/RBV).[4] Although triple-drug therapy has demonstrated substantial improvements in sustained virologic response (SVR), it has added an increased financial burden on health plans.

The additional expenditure associated with the newly approved therapies has generated a great deal of attention within the managed care industry. Health plans are striving to find appropriate strategies to help contain this additional cost without sacrificing patient outcomes. Since the approval of these new products, it has been difficult to evaluate the associated clinical and financial outcomes, as many patients require nearly a full year of therapy to achieve a SVR. However, now that a sufficient amount of time has passed, plans have an opportunity to review the utilization of these products within their patient populations and determine both the outcomes and costs associated with the new therapies.

Health Plan HCV Claims Analysis

To help quantify the impact of the two new therapies, CDMI conducted an analysis of HCV-related pharmacy claims. The purpose of the analysis was to identify discontinuation rates, costs of treatment, costs of discontinuation, and adherence rates for HCV-treated patients within a regional commercial health plan. Patients were included if they initiated HCV therapy between March 1, 2011, and July 31, 2012. Based on telaprevir and boceprevir minimum initiation and futility treatment algorithms, claims-based assumptions were developed to identify patients as discontinuing, completing, or actively on therapy. The results showed a comparable amount of patients completing therapy in both treatment groups. Additionally, the adherence rate for each product was relatively high and not statistically different between the groups. From the data identified, the major difference observed between the two treatment groups was related to cost, with

Table 1

Protease Inhibitor Claims Analysis[5]

	Telaprevir	Boceprevir
Number of patients	270 (82.8%)	56 (17.2%)
Patients actively on therapy	26 (9.6%)	12 (21.4%)
Patients discontinuing therapy	88 (32.6%)	11 (19.6%)
Patients completing therapy	156 (57.8%)	33 (58.9%)
Adherence rate	92.3%	88.0%
Mean Treatment Costs per Patient (PI Plus Pegylated Interferon)		
Cost of completion	$65,625.95	$48,086.64
Cost of discontinuation	$29,377.17	$13,877.73*

*Cost of discontinuation does not reflect patients who discontinued therapy during the four-week peg-IFN/RBV lead-in period.

the costs of discontinuation and completion of therapy being higher in patients treated with telaprevir. These results demonstrate that, due to the similar therapy completion and discontinuation rates, health plans should incorporate both the costs of discontinuation and completion of therapy when developing decision-making models for utilization management in HCV treatment.

Considerations for Managed Care

In addition to the increased financial burden, there are several other considerations that health plans should be aware of when developing management strategies for their patients with HCV. The first aspects of the new therapies that should be reviewed, prior to considering any financial impact, are the safety and efficacy profiles of these products. From an efficacy standpoint, the extent of SVR attainment appears to be relatively comparable.[6-9] This remains true when treating patients with compensated liver disease, including cirrhosis, and in patients who were previous null responders to peg-IFN/RBV therapy.[8-10] Where these products begin to demonstrate differences is in their tolerability profiles and administration requirements.

Although both medications carry warnings related to anemia, only telaprevir has a boxed warning regarding serious skin reactions.[3] Fatal and non-fatal serious skin reactions, including Stevens-Johnson Syndrome, drug reactions with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, have been reported in patients treated with telaprevir combination treatment.[3] Unique to boceprevir, the addition of boceprevir to peg-IFN/RBV therapy may result in worsening of neutropenia associated with peg-IFN/RBV alone.[2]

Aside from specific drug precautions, the administration associated with each product also varies. The treatment algorithm for telaprevir is considered to be a simpler process compared to boceprevir. Every patient who is initiated on telaprevir therapy and does not meet the futility requirements is expected to remain on therapy for 12 weeks followed by response-guided peg-IFN/RBV therapy.[3] Boceprevir requires a four-week lead-in period with peg-IFN/RBV therapy, followed by 24 to 44 weeks of response-guided boceprevir in combination with peg-IFN/RBV.[2] The four-week lead-in period is considered by many to be beneficial when treating patients with protease inhibitors. The lead-in can help to assess a patient's readiness to begin therapy and ability to adhere to his or her specific regimen; decrease the likelihood of viral relapse and resistance; predict the likelihood of achieving a SVR; and identify patients who are inappropriate for protease inhibitor therapy prior to initiating a costly medication. For both agents, the response-guided therapy is based on each patient's individual HCV-RNA results at predefined intervals of therapy. While both products should be administered with food, boceprevir requires only a light snack for appropriate absorption.[2] Telaprevir needs to be administered with 21 grams of fat per dose. Administering telaprevir on an empty stomach may result in an area under the curve (AUC) reduction of up to 73 percent.[11]

The influence that product toxicity and administration have on treatment discontinuation is an important concern when reviewing these products. Premature discontinuation of therapy completely mitigates the clinical effectiveness of these agents, is associated with increased viral resistance,

Table 2

Clinical Trial Results[6-9]

Trial	Number of Patients	Population Studied	PI Studied	Fibrosis or Cirrhosis	SVR*	Relapse Rates*	Serious Adverse Events*
SPRINT-2	1097	Treatment naive	Boceprevir	34 (9%)	63-66% vs. 38%	9% vs. 22%	11-12% vs. 9%
ADVANCE	1088	Treatment naive	Telaprevir	231 (21%)	69-75% vs. 44%	9% vs. 28%	9% vs. 7%
RESPOND-2	403	Treatment experienced	Boceprevir	78 (19%)	59-66% vs. 21%	12-15% vs. 32%	10-14% vs. 5%
REALIZE	662	Treatment experienced	Telaprevir	316 (48%)	64-55% vs. 17%	7% vs. 5%	12% vs. 5%

*Treatment vs. control groups. Data are n (%) unless otherwise indicated.

and results in a substantial amount of wasted costs for health plans. To ensure that patients have the greatest potential to achieve a SVR, the full duration of therapy—with both protease inhibitor therapy and peg-IFN/RBV therapy—must be completed. Patients need to be appropriately evaluated for their readiness to begin therapy and provided enough support to address potential barriers to adherence and enhance their likelihood of therapy completion. Helping patients complete the full duration of therapy is perhaps the greatest strategy to reduce inappropriate resource utilization associated with these products.

Another important strategy to help contain unnecessary resource utilization is to make sure that physicians are adherent to the specific futility rules that have been outlined for each product. If a patient is not responding to therapy, the medications should be discontinued, as appropriate. One barrier to successfully following the futility rules is the timeliness of HCV-RNA results. HCV-RNA results may take several days, or even more than a week in some areas, to return to the ordering physician. This presents a problem, as these medications are often distributed by specialty mail-order pharmacies. When a patient is identified as needing to discontinue therapy, there is a high likelihood that the pharmacy filling the patient's HCV medications has already shipped and billed the health plan for the next month of therapy. This is a major concern in patients being treated with telaprevir, as each month of therapy costs more than $18,000.[12] Addressing this problem will help reduce the waste associated with these therapies and ensure patients are being managed appropriately.

A final strategy to help minimize inappropriate resource utilization is to limit the use of erythropoietin-stimulating agents (ESAs) in patients being treated for HCV. As protease inhibitors increase the rate of anemia in patients with HCV, many physicians are using ESAs to control hemoglobin levels. This can be a particularly costly therapeutic intervention. A comparable alternative to the use of ESAs is to reduce the dose of ribavirin in patients experiencing anemia. This helps contain unnecessary costs and is not associated with reduction in SVR attainment.

Impact of Future HCV Therapies

Although the current treatment options available for HCV are generating a substantial amount of managed care attention, the extensive pipeline of agents on the horizon will create additional concerns for managed care within the next few years. With dozens of agents being tested in clinical trials, many of which are interferon-free, the treatment paradigm of HCV management may drastically evolve in the next five years. Although many of these agents appear to be associated with improvements in SVR, they will likely be associated with an additional financial burden on the U.S. healthcare system. These agents will likely be priced at a premium due to potential benefits in terms of safety, efficacy, and administration compared to current therapies. Additionally, there will likely be a large influx of HCV patients being initiated on treatment. This influx may be derived from the current potential warehousing of patients awaiting oral-only therapies, an increase in the amount of patients eligible for therapy who have contraindications to interferon or ribavirin, and an increase in HCV diagnosis following the recent Centers for Disease Control and Prevention recommendation to test all baby boomers. It will be important for health plans to take these factors into consideration as clinical trials for these therapies begin to approach FDA approval. It appears as though the economic burden of managing HCV will only increase as time progresses. Health plans need to be prepared with appropriate management strategies to endure the escalating costs of care.

Telaprevir Response-Guided Therapy[3,12]

	HCV-RNA Results		Treatment Schedule				
	At Treatment Week 4	At Treatment Week 12	STOP 4	STOP 12	STOP 24	48	Total Cost
Treatment-Naïve and Prior Relapsers	Undetectable	Undetectable	Telaprevir-12				$72, 400
			PegIFN + Ribavirin-24				
	Detectable	Undetectable	Telaprevir-12				$89, 600
			PegIFN + Ribavirin-48				
	Undetectable	Detectable	Telaprevir-12				$89, 600
			PegIFN + Ribavirin-48				
Prior Partial Responders or Null Responders	All Patients		Telaprevir-12				$89, 600
			PegIFN + Ribavirin-48				

In clinical trials, HCV-RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL.

Futility Rules: Week 4 or Week 12: If the patient has a HCV-RNA level greater than 100 IU/mL, then discontinue telaprevir and PR.
If at week 12, therapy with telaprevir will already be complete but PR will still need to be discontinued.
Week 24: If the patient has a detectable HCV-RNA, then discontinue PR therapy.

Boceprevir Response-Guided Therapy[2,12]

	HCV-RNA Results		Treatment Schedule						
	At Treatment Week 12	At Treatment Week 24	4	STOP 12	STOP 24	28	36	48	Total Cost
Previously Untreated	Undetectable	Undetectable		Boceprevir-24					$50,200
			PegIFN + Ribavirin-28						
	Detectable	Undetectable		Boceprevir-32					$74, 600
			PegIFN + Ribavirin-48						
Previous Partial Responders or Relapsers	Undetectable	Undetectable		Boceprevir-32					$66, 000
			PegIFN + Ribavirin-36						
	Detectable	Undetectable		Boceprevir-32					$74, 600
			PegIFN + Ribavirin-48						
Prior Null Responders	All Patients			Boceprevir-44					$89, 700
			PegIFN + Ribavirin-48						

In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL.

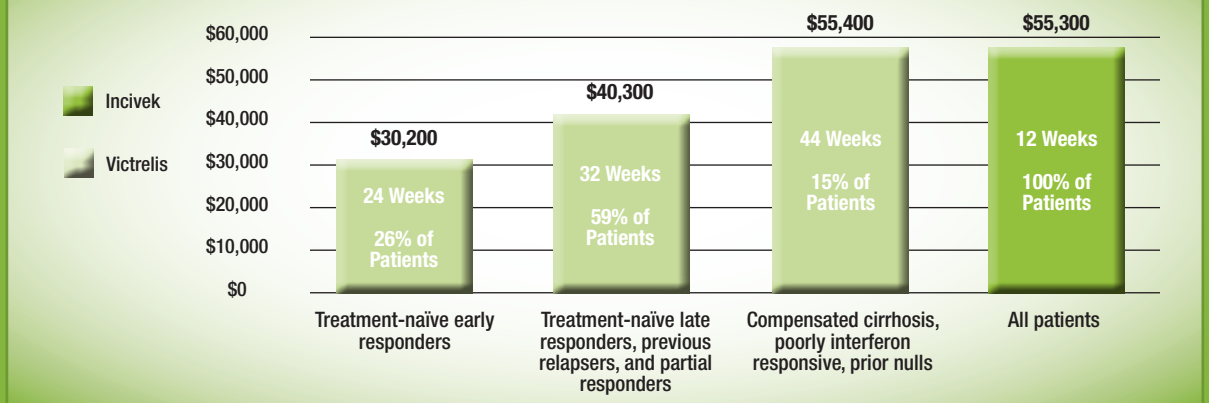
Futility Rules: Week 12: Discontinue therapy in all patients with HCV-RNA levels of greater than or equal to 100 IU/mL.
Week 24: Discontinue therapy in all patients with confirmed detectable HCV-RNA levels.

Comparing Cost

When comparing the respective costs of therapy of boceprevir and telaprevir, it is important to look beyond a simple cost per unit or cost per claim analysis. These medications vary in respect to duration of therapy, and it is important to understand the impact that this will have on pharmacy expenditure. For telaprevir, it is simpler to assess this impact as 100 percent of patients should be prescribed therapy for 12 weeks. Boceprevir, on the other hand, requires a more complex analysis to determine treatment costs. Boceprevir therapy can be prescribed for 24, 32, or 44 weeks, depending on each patient's individual HCV-RNA response. Each of these durations will be associated with different total costs.

In addition to the costs derived from the duration of therapy, it is also important to analyze the costs associated with each premature discontinuation. Even with the recent advances in pharmacotherapy, there remains a substantial number of patients who discontinue early and generate wasted costs for plans. It is important to keep these factors in mind during the formulary management decision-making process and to assess each product appropriately.

Cost/Patient Comparison[12-16]



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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

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

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

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

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

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 overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

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

Date of Issue: May 18, 2011 **Version: 3**

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

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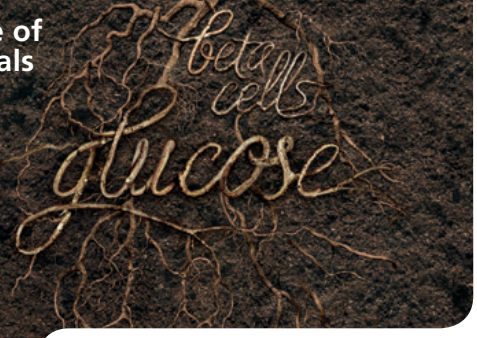
VICTOZA®
liraglutide (rDNA origin) injection

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%*



Low rate of hypoglycemia

Flexible dosing any time of day, independent of meals

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

VictozaCare™ helps patients stay on track with ongoing support
—Patients enrolled in **VictozaCare™** were more adherent to Victoza® than those not enrolled†

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

novo nordisk®

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Indications and usage

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

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

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

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

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

Important safety information

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

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

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

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.

1111-00006045-1 January 2012

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