Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Magellan Rx MANAGEMENT℠

PARTNERS RX®

The Future of Pharmacy and Medical Management

www.magellanhealth.com

PURSUING A LIFE WITHOUT BLEEDS

one person at a time

Our pursuit will continue until a life without bleeds is a reality for all.

OUR PROMISE TO YOU CAN BE SEEN IN EVERYTHING WE DO.

For more than 60 years, Baxter has consistently pursued advancements in the treatment of bleeding conditions. Through our leading investments in research, vast array of programs and support, and incredible people who are dedicated to serving you every day, we partner with you on your life's journey to strive toward our vision.

We have a bold vision for the future of bleeding conditions: "A Life Without Bleeds." We're passionate about this vision—it inspires us, motivates us, and defines us. Baxter is dedicated to doing everything we can to help make your life better by delivering cutting-edge treatments and an extensive selection of critical resources. We have 12 ongoing clinical trials, including those in hemophilia A, hemophilia B, inhibitors, von Willebrand disease, and acquired hemophilia A. For people with bleeding conditions, the future has never been brighter.

Our proven past, the advancements we're making today, and our passion for the future fuel the Baxter promise: **Our relentless pursuit continues until a life without bleeds is a reality for all.** This promise to you can be seen in everything we do, and this is what makes us the company we are.

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Compassion for Patients.™

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CDMI REPORT

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WELCOME

to this issue

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trends

Letter from Magellan Rx

Dear Managed Care Colleagues,

As many of you have already heard, CDMI has officially been acquired by Magellan Health, Inc. We are happy to announce that the integration process has already begun, and we wanted to take this opportunity to address some questions that you and your colleagues may have regarding how this will impact our business and, more importantly, our relationships with our customers.

Susan Petrovas, Magellan Rx

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

CDMI now falls under the umbrella of Magellan Rx Management. Magellan Rx Management is an integrated pharmacy organization that strives to balance industry-leading quality of care with cost-effective management strategies. In addition to CDMI, Magellan Rx Management is comprised of:

- A fully functioning PBM (formerly Partners Rx)
- ICORE Healthcare: experts in medical pharmacy management
- Magellan Medicaid Administration: servicing Medicaid programs for 25 states and D.C.

With each of the above components now integrated into one organization, we can leverage our collective scale and expertise to manage the total drug spend for our payor clients, while ensuring a clear focus on the specific clinical and financial needs of each individual customer.

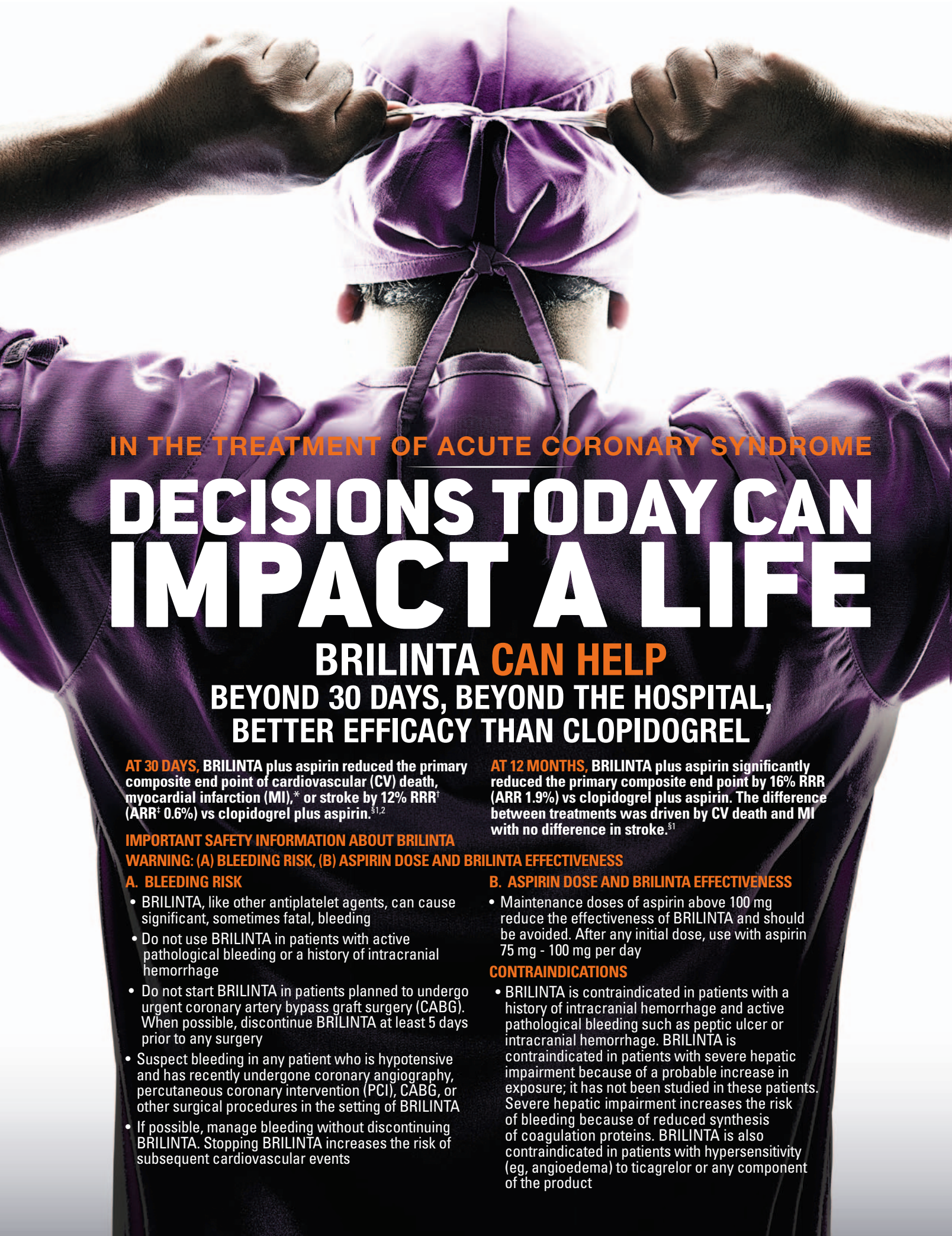
Magellan Rx Management has approached the market with a unique vision of care that better manages cost with a customer-first culture and innovative tools to provide insightful solutions. Combining our industry-leading pharmacy benefits management with specialty, medical, and more than 40 years of Medicaid experience results in effective cost management without sacrificing the quality of care delivered to our payor clients and their respective beneficiaries.

Magellan Rx Management offers a full-service platform, including customized formularies, claims processing, specialty pharmacy management, medical pharmacy management, targeted and customized clinical programs, extensive healthcare analytic services, and mail-order services. With more than 900 pharmacists, clinical case managers and customer service representatives, Magellan Rx Management is focused on the needs of our customers and is committed to providing our payor clients with the highest standard of customer service that you have come to expect.

In addition, we will remain focused on providing and executing industry-leading clinical programs that address gaps in care, Star Ratings, HEDIS measures, adherence, and more. If you have any questions regarding the integration, or any of the services offered by Magellan Rx Management, please feel free to contact me directly at **spetrovas@magellanhealth.com.** As always, I value any feedback that you may have. Thank you for reading!

Sincerely,

Susan C. Petrovas, RPh
Magellan Rx Management



IN THE TREATMENT OF ACUTE CORONARY SYNDROME

DECISIONS TODAY CAN IMPACT A LIFE

BRILINTA CAN HELP

BEYOND 30 DAYS, BEYOND THE HOSPITAL, BETTER EFFICACY THAN CLOPIDOGREL

AT 30 DAYS, BRILINTA plus aspirin reduced the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI),* or stroke by 12% RRR† (ARR‡ 0.6%) vs clopidogrel plus aspirin.§1,2

AT 12 MONTHS, BRILINTA plus aspirin significantly reduced the primary composite end point by 16% RRR (ARR 1.9%) vs clopidogrel plus aspirin. The difference between treatments was driven by CV death and MI with no difference in stroke.§1

IMPORTANT SAFETY INFORMATION ABOUT BRILINTA

WARNING: (A) BLEEDING RISK, (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

A. BLEEDING RISK

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg - 100 mg per day

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage and active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure; it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins. BRILINTA is also contraindicated in patients with hypersensitivity (eg, angioedema) to ticagrelor or any component of the product

BRILINTA®
ticagrelor tablets

PROVEN SUPERIOR TO CLOPIDOGREL IN REDUCING CV DEATH AT 12 MONTHS

CV death secondary end point: RRR with BRILINTA plus aspirin was 21% (ARR 1.1%) vs clopidogrel plus aspirin[§1]

INDICATIONS

BRILINTA is indicated to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (unstable angina, non–ST-elevation myocardial infarction, or ST-elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined end point of CV death, myocardial infarction (MI), or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin >100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin >100 mg daily.

HELP MAKE AN IMPACT WITH BRILINTA

BLEEDING AT 12 MONTHS, there was no significant difference in Total Major Bleeding (which includes Fatal and Life-threatening bleeding) for BRILINTA plus aspirin vs clopidogrel plus aspirin (11.6% vs 11.2%).

There was a somewhat greater risk of Non–CABG-related Major plus Minor Bleeding for BRILINTA plus aspirin vs clopidogrel plus aspirin (8.7% vs 7.0%) and Non–CABG-related Major Bleeding (4.5% vs 3.8%), respectively.

PLATO trial did not show an advantage for BRILINTA compared with clopidogrel for CABG-related Bleeding (Total Major 85.8% vs 86.9% and Fatal/Life-threatening 48.1% vs 47.9%, respectively).[‖1]

WARNINGS AND PRECAUTIONS

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin doses >40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

*Excluding silent MI. †RRR=relative risk reduction. ‡ARR=absolute risk reduction. §The PLATO study compared BRILINTA (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-mg to 600-mg loading dose, 75 mg daily thereafter) for the prevention of CV events in 18,624 patients with ACS (UA, NSTEMI, STEMI). Patients were treated for at least 6 months and up to 12 months. BRILINTA and clopidogrel were studied with aspirin and other standard therapies.

‖PLATO used the following bleeding severity categorization: **Major Bleed–Fatal/Life threatening**. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding. **Major Bleed–Other**. Any one of the following: significantly disabling (eg, intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2 to 3 units (whole blood or PRBCs) for bleeding. **Minor Bleed**. Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).

ADVERSE REACTIONS

- The most commonly observed adverse reactions associated with the use of BRILINTA vs clopidogrel were Total Major Bleeding (11.6% vs 11.2%) and dyspnea (14% vs 8%)
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

References: 1. BRILINTA Prescribing Information, AstraZeneca.
2. Data on file, 1755503, AstraZeneca.

AstraZeneca

BRILINTA® *(ticagrelor)* Tablets

WARNING: (A) BLEEDING RISK and (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
See full prescribing information for complete boxed warning

A. BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding [see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS].**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage [see CONTRAINDICATIONS].**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery [see WARNINGS AND PRECAUTIONS].**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgery [see WARNINGS AND PRECAUTIONS].**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see WARNINGS AND PRECAUTIONS].**

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES (14) in full Prescribing Information].**

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [*see Clinical Studies (14) in full Prescribing Information*]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS

History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [*see Clinical Studies (14) in full Prescribing Information*].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Hypersensitivity BRILINTA is contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product [*see Adverse Reactions (6.1) in full Prescribing Information*].

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [*see Adverse Reactions (6.1) in full Prescribing Information*]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [*see Warnings and Precautions (5.5)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [*see Dosage and Administration* and *Clinical Studies (14) in full Prescribing Information*].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea In PLATO, dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but occasionally required discontinuation (0.9% of patients taking BRILINTA versus 0.1% of patients taking clopidogrel). If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In the case of intolerable dyspnea requiring discontinuation of BRILINTA, consider prescribing another antiplatelet agent. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [*see Drug Interactions (7.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

ADVERSE REACTIONS

Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [*see Warnings and Precautions (5.4) in full Prescribing Information*]

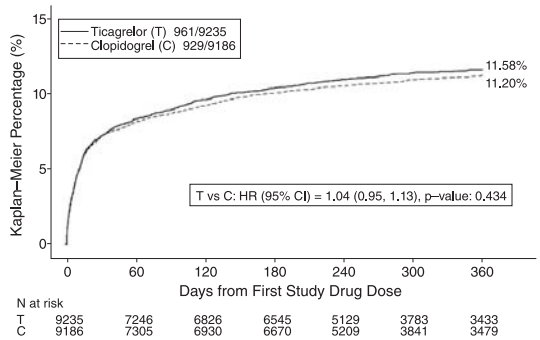
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	**Clopidogrel N=814**
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel. No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	**Clopidogrel N=9186**
Dyspnea[1]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[1] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel. Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities Serum Uric Acid: Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group). Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders – Hypersensitivity reactions including angioedema [*see Contraindications (4.4) in full Prescribing Information*].

DRUG INTERACTIONS

Effects of other drugs Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5. Ticagrelor is also a p-glycoprotein (P-gp) substrate.

CYP3A inhibitors [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

CYP3A inducers [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Aspirin Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

Effect of BRILINTA on other drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin, lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Digoxin *Digoxin:* Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Other Concomitant Therapy BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred. In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

Nursing Mothers It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of BRILINTA in pediatric patients have not been established.

Geriatric Use In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [*see Contraindications, Warnings and Precautions,* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Renal Impairment No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

[*see section (13.1) in full Prescribing Information*]

PATIENT COUNSELING INFORMATION

[*see section (17) in full Prescribing Information*]

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MANAGED CARE NEWSSTAND

Rheumatoid Arthritis Patients Face Higher Risk for Kidney Disease

Mayo Clinic researchers have found that patients with rheumatoid arthritis (RA) have a greater risk of developing kidney disease than those who do not have RA. The researchers studied 813 patients with RA and 813 without RA over a 20-year period. Their findings were published in the *American Journal of Kidney Diseases.*

They found the risk for kidney disease was one in four in the RA group and one in five in the non-RA group. Heart disease was also more common in RA patients with chronic kidney disease. Factors that increased the risk included high sedimentation rates during the first year (indicating more severe inflammation), use of corticosteroids, obesity, dyslipidemia, and high blood pressure.

The authors note that their results could impact the course of RA and the way physicians manage the disease. They recommend that clinicians test RA patients for kidney problems at least once a year and work to control RA and the associated inflammation. Other risk-reduction strategies physicians and patients should consider include controlling high blood pressure, avoiding high-salt foods, and discontinuing or reducing use of medications that can damage the kidneys.

Source: Hickson L et al. Development of reduced kidney function in rheumatoid arthritis. *Am J Kidney Dis.* 2014;63(2):206-213.

Young Skin Cancer Survivors Have Higher Risk for Future Cancers

Patients who had non-melanoma skin cancers (NMSC) have a higher risk of developing melanoma and others types of cancers in future years, according to a British study. The risk is even higher in NMSC patients under the age of 25.

Researchers found that patients who had NMSC were 1.36 times more likely to develop other cancers than those who did not have NMSC. The risk increased dramatically in NMSC patients under the age of 25, who are 23 times more likely to develop cancer overall. More specifically, patients in the younger group were 94 times more likely to develop melanoma and 93 times more likely to have salivary gland cancer.

The researchers said younger patients diagnosed with NMSC may benefit from targeted screenings for internal tumors because of their increased risk for cancers.

Source: Ong E et al. Subsequent primary malignancies in patients with nonmelanoma skin cancer in England: A national record-linkage study. *Cancer Epidemiol Biomarkers Prev*. 2014:23;490.

Patients with Hepatitis C and HIV Have Higher Rates for Serious Liver Disease

Researchers from the University of Pennsylvania report that patients with both hepatitis C and HIV face a much higher rate of serious liver disease than patients with hepatitis C alone. The researchers examined the medical records of more than 10,000 patients receiving care from 1997 to 2010. The patients had hepatitis C alone or had both hepatitis C and HIV.

They found the risk for serious liver disease was 80 percent higher in patients with hepatitis C and HIV. Co-infected patients taking antiretroviral therapy (ART) that controlled their HIV had a 60 percent higher rate of serious liver disease when compared with those who had hepatitis C alone. That finding was somewhat surprising because it was thought that ART may slow the liver fibrosis associated with hepatitis C. The rates of serious liver disease were higher in co-infected patients with these risk factors: advanced liver fibrosis, diabetes, severe anemia, and non-black race.

The researchers said that physicians should consider starting hepatitis C treatment sooner in patients with both conditions, especially those with advanced liver disease, to reduce the risk for serious liver complications.

Source: Re V et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus–monoinfected patients: A cohort study. *Ann Intern Med*. 2014;160(6):369-379.

New Drug Effective for Drug-Resistant Lung Cancer in Phase 1 Trial

The new drug ceritinib may offer hope to lung cancer patients who become resistant to crizotinib. Fifty-nine patients with ALK-positive non-small cell lung cancer (NSCLC) participated in the phase 1 study and received escalating doses of ceritinib. Researchers evaluated patients to determine the drug's safety, pharmacokinetic properties, and effect on tumors. During an expansion phase of the study, an additional 71 patients participated.

Researchers found that the drug was well tolerated, with only mild adverse events that stopped after treatment stopped or the medication was reduced. In addition, they found ceritinib was effective against NSCLC tumors that had become resistant to crizotinib, as well as those that had never been treated with crizotinib.

Based on earlier results, ceritinib received "breakthrough therapy" designation from the U.S. Food and Drug Administration (FDA) last year. Novartis Pharmaceuticals, the drug's manufacturer, has applied to the FDA for accelerated approval based on these latest findings.

Source: Shaw A et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *NEJM*. 2014; 370:1189-1197.

Psoriasis Therapies Face Stiffer Competition

There are more and more therapeutic options for patients with moderate to severe plaque psoriasis. Three new classes of drugs will soon be available, including interleukin-17 (IL-17) inhibitors and two oral therapies: a janus kinase (JAK) inhibitor and a phosphodiesterase-4 (PDE-4) inhibitor.

According to a recent analysis from Frost & Sullivan entitled "Product and Pipeline Analysis of the Global Psoriasis Therapeutics Market," at least 37 investigational drugs are in various stages of development for moderate-to-severe psoriasis. With so many options available to consumers, drug companies will have to compete with one another to demonstrate the superiority of their therapies.

"If the cost and safety profiles are comparable, therapies that offer better patient convenience will be preferred to improve adherence to therapy and prevent relapse," the report stated. "Advanced devices and improvements in formulations to reduce the inconvenience of frequent injections could set otherwise similar products apart in the eyes of patients."

Source: Frost & Sullivan report. Emerging psoriasis therapies go head-to-head with marketed drugs to win over physicians, patients and payers. News release. 29 April 2014.

Gene Panel Screens for Key Cancer-Associated Mutations

Stanford University School of Medicine researchers conducted a study of nearly 200 women using a multiple gene panel to assess the sequences of 42 genes known to be associated with breast and other cancers. The women in the study had previously undergone testing for BRCA1 and BRCA2, tests often performed to identify women's cancer risk.

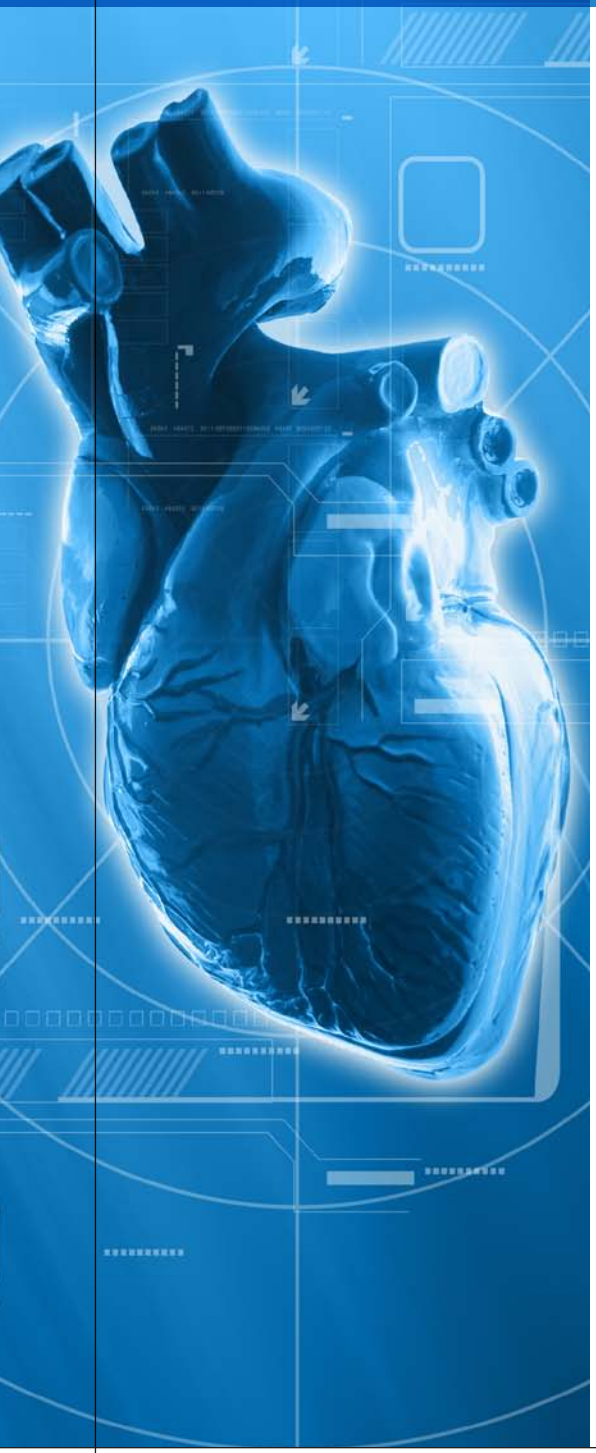
Though the women did not have mutations in these genes, researchers found that as many as 10 percent of them—specifically, those who had a personal or family history of breast or ovarian cancer—had another genetic mutation related to cancer that could potentially lead to changes in their care.

Whole genomic testing may be right for some patients. But the researchers say gene-panel sequencing may offer a more affordable option between whole genomic testing and testing for a single gene, such as BRCA1 or BRCA2, for certain groups of patients.

Source: Kurian A et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol*. 14 April 2014. Epub ahead of print.

Implantable Cardioverter Defibrillators: Reassessing the Indications and Costs

David Wolinsky, MD, FACC, FASNC, Section Head, Nuclear Cardiology, Robert and Suzanne Tomisch Department of Cardiology, Cleveland Clinic Florida; and Debra Gordon, MS



David Wolinsky, MD, FACC, FASNC

An estimated 5.1 million people in the United States have been diagnosed with heart failure, a condition that contributes to one in nine deaths in this country. Heart failure is one of the few cardiovascular conditions whose incidence has not dropped in the past 20 years; in fact, given the aging population and continued success at reducing the death rate from other cardiovascular conditions, the incidence is expected to rise 46 percent over the next two decades.[1]

That comes at a tremendous cost. In 2012, total costs for heart failure were estimated at $30.7 billion, 70 percent of that related to direct medical costs. By 2030, the total cost is expected to increase 127 percent to $69.7 billion, or about $244 for every American adult. Sudden cardiac death (SCD) is a leading cause of mortality in patients with left ventricular dysfunction, heart failure, or both.[2]

Implantable cardioverter-defibrillators (ICDs), which deliver shocks to patients with ventricular arrhythmias to restore a normal heartbeat, have significantly reduced the risk of SCD. Consequently, the use of prophylactic ICD implantation (primary prevention) in patients with heart failure has grown exponentially since the 1990s, with more than 100,000 implanted in the United States each year.[3,4]

A 2010 meta-analysis found that ICDs reduced the risk for arrhythmic mortality by 60 percent in those patients with left ventricular ejection fraction (LVEF) less than 35 percent, and who were at least 40 days from a myocardial infarction (MI) or at least three months from coronary revascularization (95 percent confidence interval [CI]: 0.27–0.67). The relative risk of all-cause mortality was reduced by 27 percent (95 percent CI: 0.64–0.82).[5] The criteria used formed the basis of the 2013 guidelines for ICD and cardiac resynchronization therapy issued from eight leading cardiovascular organizations, including the American Heart Association and the American College of Cardiology.[6]

However, at a cost of between $48,000 and $100,000 for the surgery and hospitalization—plus significant complication rates and long-term expenditures for follow-up care and device replacements—

ICDs impose a substantial financial burden on payors.[7] Table 1 (below) highlights the costs of the devices, surgery, and follow-up care. Coupled with concerns about their appropriate use in various patient populations, there clearly is a need for improved risk stratification in determining which patients can most benefit from prophylactic ICD implantation.

Effectiveness of Implantable Cardioverter-Defibrillators

The effectiveness of ICDs was first demonstrated as secondary prevention in high-risk patients. A meta-analysis of the three landmark trials (the Antiarrhythmics vs. Implantable Defibrillators [AVID] trial, the Cardiac Arrest Study Hamburg [CASH], and the Canadian Implantable Defibrillator Study [CIDS]) found a 50 percent reduced risk for arrhythmic death with the device compared with medical therapy, and a 28 percent reduced risk for overall death.[8]

Eight large trials supported the use of ICDs for primary prevention, with a meta-analysis finding a 45 percent reduced risk for arrhythmia-related death, although the risk of all-cause mortality varied based on the patient population studied.[9] In addition, two trials demonstrated no significant reduction in two-year mortality compared with the control population.[10]

When evaluating the results of the landmark studies, it is important to note that they were conducted with single-chamber lead ICDs, in which the lead is attached to the right ventricle. Today, patients are more likely to receive a dual-chamber ICD, in which leads are also attached to the right atrium to provide atrioventricular synchronization.

Studies suggest that double-chamber devices have significantly higher complication rates.[11,12] In addition, a national sample found that 60 percent of patients receiving dual-chamber ICDs for primary prevention did not have a pacing indication.[12] There are also significant geographic differences in their use that are unrelated to patient characteristics.[13]

A retrospective cohort study of Medicare claims for ICD implantation in patients without a pacing indication found lower rates of complications with single-chamber devices, although there was no change in mortality or hospitalization risk at one year. Given the higher risks of dual-chamber devices and their higher cost, the authors questioned their preferential use in this population and called for better risk stratification in patients receiving ICDs.[11]

Cost Effectiveness of ICDs

The cost effectiveness of ICD therapy varies depending on the clinical trial reviewed, the type of ICD used, the method of insertion, and the duration of the follow-up study.[14] The short-term cost-effectiveness tends to exceed the greater than $50,000 incremental cost-effectiveness ratio (ICER) typically considered acceptable.[14] After several years, however, the ICER falls to an acceptable range.[14-17]

Risk stratification is key when considering cost effectiveness. A 2002 report found that ICD therapy in patients with a high risk of SCD but a low risk of non-sudden cardiac death was cost effective, while the benefits and cost effectiveness were substantially lower

Table 1 Resource Use and Cost Inputs of Implantable Cardioverter Defibrillators[52]

Description	Cost Mean/Median (SE)	Source
ICD implant cost (DRG 226 and 227)	$41,486 ($1,036)	AHRQ 2013
ICD generator replacement cost (DRG 245)	$31,547 ($1,544)	AHRQ 2013
Frequency of generator replacement (years)	5.0 (0.5)	Sanders 2005
ICD lead procedure cost (DRG 265)	$19,139 ($877)	AHRQ 2013
Rate of ICD lead procedure (% per year)	0.8% (0.09%)	Rordorf 2013
Cost of ICD evaluation (CPT 93295 and 93296)	$91 ($5)	CMS 2013
Frequency of ICD evaluation (per year)	3.0 (0.5)	Wilkoff 2008
Cost of ICD inappropriate shock evaluation	$2,008 ($100)	AHRQ 2013
Frequency of inappropriate shocks (PPPY)	2.8% (0.6%)	Poole 2008
Heart failure follow-up costs (per month)	$1,208 ($63)	Reed 2011
End-of-life costs (final six months of life)	$43,757 ($282)	Unroe 2011

*The costs and frequencies included in the above table are largely based on estimates and assumptions from available literature.

SE=standard error; **ASP**=average sales price; **ICD**=implantable cardioverter defibrillator; **CPT**=Current Procedural Terminology; **DRG**=diagnosis-related group; **PPPY**=per patient per year

in patients with lower ratios of sudden to non-sudden cardiac deaths.[18] Patients likely to die sooner of pump failure have less of a benefit from ICD implantation.

Another analysis used $75,000 or less per quality-adjusted life-years (QALY) to evaluate cost-effectiveness in a population with prior MI and no sustained ventricular arrhythmia. The authors found that the cost-effectiveness of ICD therapy over the patient's lifetime when compared to amiodarone barely met the criteria for those with LVEFs of 30 percent or less ($71,800/QALY). In addition, it was not cost effective in those with LVEFs of 31 to 40 percent ($195,700/QALY, and $557,900/QALY, respectively).[16]

Meanwhile, an analysis of the primary prevention trials questioned the cost effectiveness of ICD therapy in patients 65 years or older, calling for more research in this population.[19]

A major contributor to ICD costs is generator replacement. In a recent study of 231 patients, one-fourth of patients who initially met the criteria for primary prevention ICDs no longer met the criteria at replacement. Another 34 percent had not received any appropriate ICD therapies (i.e., shocks or anti-tachycardia pacing) and had not had follow-up testing of ejection fraction. The authors conclude that explanting rather than replacing devices in patients without ICD indications would save $1.6 million, which translated into a $4.05 billion savings when extrapolated over the entire ICD patient population.[20]

Appropriate Patient Selection Is Challenging

Clinicians have questioned the appropriate use of ICD therapy for SCD prophylaxis for more than a decade, calling for better risk stratification to reduce the clinical and economic repercussions of inappropriate use.[10,20-25]

In a controversial paper published by Duke Clinical Research Institute (DCRI), an analysis of the National Cardiovascular Data-ICD Registry base from 2006–2009 concluded that one-fifth (22.5 percent) of patients who received ICDs did not meet the evidence-based criteria of the time. These patients were significantly more likely to die in the hospital and to have post-procedural complications than those receiving evidence-based care (Table 2, at right).

In addition, the authors found substantial variation between hospitals in the use of evidence-based guidelines to determine appropriate patient selection for ICD.[26]

In late 2010, the U.S. Department of Justice announced an investigation in the appropriateness of ICD therapy, although the investigation was not related to the 2011 study.[27] The results of that investigation are still pending, although it has, apparently, led to more stringent assessments prior to implantation and an overall decrease in the use of ICDs.[28]

The current guidelines for the diagnosis and management of heart failure were updated in 2013 with no significant changes in the indications for ICD therapy. The guidelines recommend ICD management for primary prevention of SCD in patients with stage C heart failure, who have a life expectancy of more than one year, and an LVEF of 35 percent or less, and New York Heart Association (NYHA) Class II or III. In addition, the guidelines note that ICD therapy may be appropriate in certain patients with stage B heart failure, but call for ICD deactivation in patients with stage D.[6] The Centers for Medicare & Medicaid Services (CMS) coverage guidelines are similar.[29]

However, several of the primary prevention studies found no benefit from ICD therapy in patients with LVEF more than 25 to 30 percent. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) only demonstrated a benefit over medical therapy in patients with LVEF of 25 percent or less, while the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study found a benefit only in patients with an NYHA Class II. The trials also evaluated ICD insertion from six months to several years after the primary MI, with little

Table 2 Non-Evidence-Based ICD Implantation[26]

22.5 percent	for non-evidence-based indication
36.8 percent	implanted in patients within 40 days of MI
3.2 percent	implanted in patients within three months of coronary artery bypass surgery
12 percent	implanted in patients with NYHA Class IV symptoms
62.1 percent	implanted in patients with newly diagnosed heart failure

benefit shown in those who were less than 18 months out. Current guidelines, however, set 41 days post-MI as a standard.[6]

Conversely, several studies point to the underuse of ICD therapy, particularly in women and minorities.[30-32] The studies all suggest further research is needed in determining who will most benefit from ICD implantation.

In addition, the guidelines rely almost solely on ejection fraction as the risk-stratifying indicator for primary ICD implantation. It is well known that there is significant variability to ejection fraction according to technique used—echocardiography, radionuclide angiography, gated SPECT, invasive left ventriculography, or cardiac MR. There is significant intra- and inter-observation variation associated with all of these techniques.[33-35]

Questions have also been raised regarding the clinical and ethical aspects of ICD replacement, with a 2012 editorial in the *New England Journal of Medicine* calling for a thorough reevaluation of the clinical data for patients who require ICD replacement.[4]

Getting to Better Risk Stratification

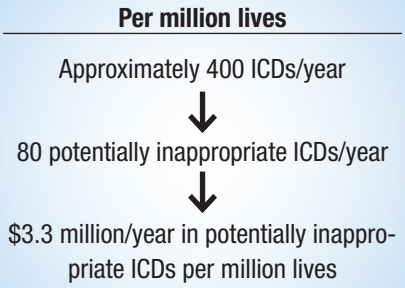
As previously noted, ICD therapy is more cost effective when used in populations most likely to benefit. Figure 1 (below) depicts the potential costs attributed to inappropriate ICDs per million lives.

Identifying the most appropriate patients for ICDs requires improved approaches to risk stratification that go beyond LVEF.[14]

These factors include the patient's age (worse outcomes are seen in those 70 and older), prognosis (ICD implantation is not recommended in those with a life expectancy of less than one year), functional status and baseline quality of life, type of cardiovascular disease, residual ischemic burden, and the presence of medical co-morbidities (in particular, patients with renal failure, chronic obstructive pulmonary disease, peripheral vascular disease, and diabetes with microvascular complications tend to have worse outcomes).[14,45]

Several risk-assessment models that go beyond ACC/AHA recommendations have been proposed. An analysis of data on 45,000 Medicare beneficiaries who received an ICD for primary prevention between 2005 and 2007 found seven clinically relevant predictors of mortality: 75 years of age or older, NYHA III, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, LVEF of 20 percent or less, and diabetes.[46] Another model used age, BUN, NYHA class, QRS duration, and atrial fibrillation to screen patients with low LVEF and found no benefit

Figure 1: Inappropriate ICD Utilization and Costs



Risks of Implantable Cardioverter Defibrillators

Studies find that up to one-fourth of patients with an ICD experience inappropriate shocks, which significantly impacts their quality of life as well as morbidity and mortality. Other potential complications include pacing issues, triggering of arrhythmias after cardiac resynchronization therapy, and hardware malfunction leading to device recalls, which require lead extraction.[3] A 2006 study found a 10 percent complication rate in a Medicare population, with a mean cost of $42,184 and a mean hospital stay of 4.7 days.[38]

In addition, most patients will need at least one ICD replacement over their lifetime, with 40 percent requiring two. This, in turn, may result in additional complications and costs.[39-42]

However, the recently approved subcutaneous ICD, which avoids the risks for transvenous lead implantation, may substantially reduce that replacement and complication rate due to stronger wires and leads that are easier to remove in case of malfunction.[43] It also appears to result in fewer inappropriate shocks.[44]

However, these devices are more expensive than traditional ICDs, thus their cost effectiveness has yet to be evaluated.

in patients with no risk factors, but a 49 percent reduction in the risk for death in those with one or more risk factors.[47]

The FDA recently approved the use of 123 iodine *meta*-iodobenzylguanidine (^{123}I-*m*IBG) cardiac scintigraphy imaging as a screening tool to assist in the evaluation of patients with NYHA Class II or Class III heart failure and left ventricular ejection fraction (LVEF) of 35 percent or less.[48]

MIBG can assess alterations in myocardial sympathetic nerve activity by highlighting norepinephrine update. Increased sympathetic activity significantly contributes to ventricular arrhythmias and SCD.[49]

The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study evaluated the prognostic role of ^{123}I-*m*IBG scintigraphy in patients with NYHA Class II or III heart failure and an LVEF of 35 percent or less. It confirmed that poor uptake of ^{123}I-*m*IBG, a heart/mediastinum ratio (H/M) of less than 1.6, predicted a poor prognosis in these heart failure patients. The hazard ratio was linear and continuous in predicting heart failure progression, arrhythmic event, and cardiac death. Multivariate analysis showed that late H/M ratio remained statistically significant when compared to plasma BNP level, NYHA class, and LVEF.[49,50]

A cost-effectiveness analysis of ADMIRE-HF and its extension trial, ADMIRE-HFX, found that screening five patients with ^{123}I-*m*IBG scintigraphy could prevent one ICD implantation, saving an estimated $5,459 over two years and $13,492 over 10 years per screened patient, respectively, with similar mortality outcomes.[51]

One drawback to the use of ^{123}I-*m*IBG is a lack of standardization of imaging procedures.[52] Further research will define the role of SPECT imaging and washout when added to the standard four-hour delayed planar images to calculate H/M.

Conclusion

Despite numerous randomized clinical trials on the utility of ICDs as primary prevention in patients with cardiomyopathy, it remains unclear which patients are most appropriate for the therapy in a real-world setting. Current guidelines rely on LVEF, while studies find that other considerations, including age and comorbidities, also impact morbidity.

Given the high cost of ICDs, as well as their impact on patient quality of life, clinicians should consider factors beyond LVEF, including overall clinical status and comorbidities, heart failure risk assessment models, and myocardial sympathetic activity when choosing the most appropriate patients for ICD therapy.

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

Drugs that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended *[see Clinical Pharmacology]*.

Drugs that Inhibit or Induce CYP3A4

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3 fold in healthy volunteers *[see Clinical Pharmacology (12.3)]*.

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of XTANDI and should be avoided if possible *[see Clinical Pharmacology]*.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring *[see Clinical Pharmacology]*.

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

Pregnancy- Pregnancy Category X *[see Contraindications]*.

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. XTANDI 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 XTANDI.

Nursing Mothers

XTANDI is not indicated for use in women. It is not known if enzalutamide 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 XTANDI, 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 XTANDI in pediatric patients have not been established.

Geriatric Use

Of 800 patients who received XTANDI in the randomized clinical trial, 71 percent were 65 and over, while 25 percent were 75 and over. No overall differences in safety or effectiveness were observed between these 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 Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic castration-resistant prostate cancer and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed *[see Clinical Pharmacology]*.

Patients with Hepatic Impairment

A dedicated hepatic impairment trial compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Baseline severe hepatic impairment (Child-Pugh Class C) has not been assessed *[see Clinical Pharmacology]*.

---------- OVERDOSAGE ----------

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizures following an overdose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4- and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (PATIENT INFORMATION).

- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- Inform patients receiving a GnRH analog that they need to maintain this treatment during the course of treatment with XTANDI.
- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.
- Inform patients that XTANDI may cause dizziness, mental impairment, paresthesia, hypoesthesia, and falls.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Apprise patients of the common side effects associated with XTANDI: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
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MEDIVATION

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MEDIVATION

For the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel

Xtandi (enzalutamide) capsules

18.4 MONTHS MEDIAN OVERALL SURVIVAL VS 13.6 MONTHS WITH PLACEBO

AND...

- 37% reduction in risk of death vs placebo ($P < 0.0001$; HR = 0.63 [95% CI, 0.53-0.75])[1]
- XTANDI can be taken with or without food[1]
- Patients were allowed, but not required, to take glucocorticoids[1]
  - In the clinical trial, 48% of patients in the XTANDI arm and 46% of patients in the placebo arm received glucocorticoids[1]
- Oral, once-daily dosing[1]
- The rate of grade 3 and higher adverse reactions with XTANDI was 47% vs placebo at 53%[1]
- Seven patients (0.9%) out of 800 treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo[1]

AFFIRM: A phase 3, global, placebo-controlled, randomized study of patients with mCRPC who previously received docetaxel[1]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include enzalutamide (XTANDI) with a category 1 recommendation for use following docetaxel in patients with mCRPC.[2]

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel.

Important Safety Information

Contraindications XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Warnings and Precautions In the randomized clinical trial, seizure occurred in 0.9% of patients on XTANDI. No patients on the placebo arm experienced seizure. Patients experiencing a seizure were permanently discontinued from therapy. All seizures resolved. Patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizure were excluded from the clinical trial. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Adverse Reactions The most common adverse drug reactions (≥ 5%) reported in patients receiving XTANDI in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% grade 3-4) and in 6% of patients on placebo (no grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients and 2% of patients on placebo. One percent of XTANDI patients compared to 0.3% of patients on placebo died from infections or sepsis. Falls or injuries related to falls occurred in 4.6% of XTANDI patients vs 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients and included non-pathologic fractures, joint injuries, and hematomas. Grade 1 or 2 hallucinations occurred in 1.6% of XTANDI patients and 0.3% of patients on placebo, with the majority on opioid-containing medications at the time of the event.

Drug Interactions: Effect of Other Drugs on XTANDI Administration of strong CYP2C8 inhibitors can increase the plasma exposure to XTANDI. Coadministration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If coadministration of XTANDI cannot be avoided, reduce the dose of XTANDI. Coadministration of XTANDI with strong or moderate CYP3A4 and CYP2C8 inducers can alter the plasma exposure of XTANDI and should be avoided if possible. **Effect of XTANDI on Other Drugs** XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is coadministered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

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

Learn more at XtandiHCP.com ❯

References: 1. XTANDI [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc; 2012. **2.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.1.2013. © National Comprehensive Cancer Network, Inc 2013. All rights reserved. Accessed December 20, 2012. To view the most recent and complete version of the guidelines, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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Immune Globulin Therapy: Solutions for Managing Inappropriate Utilization

Steve Marciniak, RPh, Associate Vice President, Pharmacy Programs, Priority Health

Haita Makanji, PharmD, Vice President, Clinical Specialty Solutions, Magellan Rx Management

The use of intravenous immune globulin (IVIG) therapy in the United States is steadily increasing as it continues to be used for more indications. While immune globulin (Ig) therapy is approved by the U.S. Food and Drug Administration (FDA) for six indications, these disease states account for only half of the total IVIG utilization.

Due to the lack of consensus guidelines on the use of IVIG, there is a significant amount of off-label utilization. The approximate annual cost of IVIG therapy is $40,000 to $90,000 per patient. Inappropriate utilization results in an unnecessary but significant burden on the healthcare system.[1]

CDMI (now a division of Magellan Rx Management) recently launched an IVIG Utilization Management Program on behalf of a large regional health plan. The primary focus of the program is to reduce the inappropriate utilization of IVIG through clinically-enhanced prior authorization reviews. Preliminary results of the program are remarkable and can provide solutions to other payors who also experience challenges managing the costs associated with IVIG.

Steve Marciniak, RPh

Haita Makanji, PharmD

Identifying Inappropriate IVIG Utilization

Diagnosis and Evidence for Use

Due to the high frequency of off-label IVIG utilization, payors face several challenges when attempting to identify inappropriate use. A significant portion of off-label IVIG is used for autoimmune and neurological conditions, which have limited evidence, and undefined treatment durations and doses. The clinical presentation for many of these conditions is similar, and signs and symptoms are often difficult to differentiate. There is often no clear evidence that IVIG therapy will even be effective. As a result, this dilemma poses a key challenge for both payors and providers.

There are several ways to control and ensure the appropriateness of IVIG therapy. The use of prior authorization is the most common method used to manage IVIG therapy; however, there are many opportunities to improve this approach and further control the exponentially increasing costs. Prior

Optimizing a patient's IVIG dose is beneficial to both the member and the health plan. Preventing a "more is better" dosing strategy through the prior authorization criteria helps ensure utilization of the lowest effective dose.

authorization criteria can mandate appropriate diagnosis prior to the initiation of IVIG therapy. Verification of the diagnosis should be evaluated by performing a thorough history and examination, referring the patient to a specialist and/or performing the appropriate laboratory assessments specific to the disease state. Documentation of previously failed treatments should also be incorporated into an IVIG prior authorization policy. To further streamline the prior authorization review process, extensive medical policies should be formulated that outline approved versus non-approved indications and essential criteria based on available medical literature.

Documenting and Monitoring Improvement

An additional obstacle in identifying inappropriate IVIG utilization is the determination of clinical improvement and/or treatment success when reauthorizing therapy. Similar to the challenges faced when justifying the initial IVIG request (i.e., non-definitive diagnosis, lack of guidelines, etc.), reauthorizing treatment can be difficult as well. Patient progress notes often lack the evidence to prove that IVIG therapy was effective for the patient. Furthermore, non-standardized reporting methods, due to the lack of consensus among providers and thought leaders, compound this problem even more.

Whenever possible, emphasis should be placed on objective measures of patient response. Tests capable of measuring functional improvement (e.g., Medical Research Council [MRC] Muscle Grading Score and electromyogram [EMG]), degree of neuropathy, IgG trough levels, and improvements in infection rates are examples of valuable tools for providers and managed care professionals. In addition, formulated medical policies should clearly outline conditions that will likely require ongoing treatment versus conditions that will require only temporary treatment for a set duration.

Options for Denied Claims

With the implementation of rigid prior authorization criteria and increased documentation requirements, discontentment among providers can be expected. Giving the providers an option for appealing a request following a claim denial is essential in maintaining positive professional relationships and assuring that appropriate patients are receiving treatment. Designing the approval process that allows for a dialogue between the prescriber and the health plan may be advantageous for all three stakeholders: payor, provider, and patient. Discussing reasons for denial (e.g., better treatment options available, inappropriate dose, etc.) and presenting the opportunity to resubmit a claim once all criteria have been met can strengthen the overall authorization process.

Health plans may also wish to facilitate peer-to-peer discussions between the provider and key opinion leaders (KOLs) as a means of reviewing complex patient cases. The ability to offer this type of service with KOLs is valuable since it incorporates an objective third-party expert in the field.

Managing High Doses and High Frequencies

Optimizing a patient's IVIG dose is beneficial to both the member and the health plan. Preventing a "more is better" dosing strategy through the prior authorization criteria helps ensure utilization of the lowest effective dose. This strategy helps minimize adverse effects associated with overdosing. Regimens with high doses and/or frequency place patients at an increased risk for consequences associated with high serum IgG trough levels, including renal, neurological, dermatological, and hematological adverse events. Rare but serious thromboembolic events due to elevated coagulation factor XI as a result of high IgG trough levels have been reported.

In addition, IVIG dose optimization helps guide treatment decisions in a manner that optimizes healthcare resources. If IVIG therapy is not successful, the provider can

advance to other treatment options rather than expend time and personnel pursuing a higher dose and/or higher frequency that may not deliver clinical improvement.

Diagnoses especially susceptible to inappropriately high doses and/or high frequencies are primary immunodeficiency, autoimmune, and neurological conditions. When managing patients with a primary immunodeficiency, the dose and frequency should be evaluated in conjunction with IgG trough levels and patient response. Often a dose range is supported by treatment guidelines. Implementing requirements for starting doses at the lower end and monitoring for response is a useful and prudent approach. Monitoring the patient's IgG trough level is another means of gauging appropriateness of a dose. For example, once a patient achieves an IgG trough level at or above the target (800mg/dL), increasing the dose may not necessarily provide additional benefit.

When using Ig therapy to treat neurological conditions, enforcing dosage limits is challenging due to clinical evidence supporting high-dose IVIG. For these patients, the emphasis is on documentation of improvement and stabilization of the condition. Provider progress notes demonstrating sustained results may be an indication that the patient is responding and stable, and that a trial of a dose and/or frequency reduction may be appropriate.

Impact of Site of Care

The choice of site of care provides an important role in IV therapy due to safety, efficacy, and potential cost reduction opportunity. Since the majority of Ig-related adverse events occur during the first infusion or during a change from one Ig product to another, the American Academy of Allergy, Asthma, and Immunology (AAAAI) has recommended that all initial infusions of Ig therapy be provided under physician supervision in a facility equipped to handle the most severe acute medical complications.[2] Once patients have tolerated Ig therapy, preferred site-of-care settings should be considered. Therefore, steering eligible patients to a preferred site-of-care setting would provide a viable cost-saving measure. A preferred site of care would be able to provide the patient with more individualized and patient-centric care while also providing the payor with an opportunity to maximize savings and establish a beneficial relationship among all parties involved.

A claims and financial expenditure analysis was recently conducted within a regional health plan to investigate the appropriateness of IVIG dosing and site of care. A total of 187 unique patients were administered Ig therapy during the measurement period, representing 964 total claims and $5.5 million; mean age: 49.4; female: 59.9 percent. Of the 964 Ig claims, 359 (37.2 percent) were administered in patients' homes with an average paid amount per claim of $4,584.17; 185 (19.2 percent) were administered in an outpatient physician office with an average paid amount per claim of $2,912.30; 420 (43.6 percent) were administered in an outpatient hospital setting or unidentifiable setting with an average paid amount per claim of $7,932.23. Average paid amount per member was $27,893.53, $13,469.40, and $33,651.87, respectively.

Ig infusion in an outpatient hospital setting had an average cost per Ig claim that was 172 percent more than if administered in an outpatient physician office. This cost could be easily managed by establishing preferred sites of care and steering the appropriate patients to these sites.

Initiation of an IVIG Program

In the case of one health plan, CDMI's clinical management of IVIG has yielded $154,000 in savings within the first 10 weeks of program initiation. The enhanced clinical focus on appropriate use and dose optimization, along with pharmacist-led discussions with providers and KOLs, has enabled the program to achieve tremendous success in a relatively short period of time. Integration of CDMI pharmacists into the prior authorization infrastructure of the health plan allows for turn-key implementation and subsequent cost savings.

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Top Health Plan Pharmacy Issues and Hidden Opportunities for Managing Medication Costs:
A Solid Benefit Guidance Perspective

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Health plans—both large and small—have the common desire to maintain top-notch pharmacy performance in operational, financial, and clinical aspects. In working with health plan pharmacy directors and their staff, Solid Benefit Guidance (SBG) has observed the following key areas in which taking a deeper review into the plan's operational, clinical, and unique organizational processes will identify hidden opportunities for either quick win (low-hanging fruit) improvements or long-term strategies that will enhance their capabilities for effective and efficient pharmacy management programs. The top areas that we largely encourage plans to focus their time and efforts include:

- Specialty medication benefits
- Audit and risk mitigation
- Clinical programs assessment

It is well recognized that high-cost specialty medications continue to have a huge impact on medication cost trends. Plans have significant opportunities to uncover their key drivers of specialty prescription medication spend and identify and quantify their specialty medication costs under the medical benefit. Complicating the capacity to perform these analyses are analytics that are generally underdeveloped and issues of complex and inconsistent billing practices, without controls under the medical benefit. This is also compounded by confusion as to which specialty costs are paid through the medical versus prescription medication benefit.

SBG recommends that plans focus on developing standard specialty medication reporting templates across the medical and prescription benefits, along with the necessary analytics to gather data and codes that will allow the translation of this information for decision support and medication management. This is the first critical step in getting a true grasp on the specialty medication spend and related services.

Effective reporting is the first step toward a comprehensive view and understanding of key cost drivers and opportunities of where to best focus limited resources for specialty medication strategies. With established, routine reporting, issues with outlier claims billing become more readily apparent. Plans are able to implement quick-win strategies generally focused on providers using inconsistent billing units for specialty medications or selective implementation of HCPCS limits on medical codes that protect against gross billing errors. Long-term, these routine analyses prove beneficial for plans to spot opportunities in working closely with service providers for negotiating contracts for preferred provider site-of-care networks, specialty pharmacies, and manufacturer rebates that recognize specialty medications across the medical and prescription benefit continuum.

Audit/Mitigation Strategies

With annual pharmacy budgets that often run in the millions or billions of dollars, it is inevitable that a plan's pharmacy services will be subject to an audit of some kind. Current best practice for health plans is to conduct an independent audit of processes and procedures, as well as stage mock audits that can instill a mindset of audit readiness for department staff.

Areas most often targeted for audit activities are listed in Table 1 (below). Routine focus on these areas for audit activities will often reveal a plan's key risk areas for corrective action planning and mitigating their downstream risks.

Of the various audit activities conducted, compliance audits rise to the top for every Medicare health plan. Medicare plans and providers face a crucial task each year to be at top-notch performance for quality and compliance in order to remain competitive. With major revenue at stake, plans continue to focus heavily on maximizing their performance and may enlist external audit services for an objective assessment to assure their CMS compliance and that staff is up to speed on CMS regulatory requirements.

Table 1 Target Areas for Audit Activities

Area of Focus	Audit Activity	Examples of Key Risk
Compliance Audit	Assess company's level of compliance with operating procedures as defined by regulatory or contractual arrangements Employ mock audits to simulate real-life audit scenarios and situations	Part D Plan compliance with CMS regulations pertaining to: • Operations • Service level performance • Formulary administration • Fraud, waste, and abuse • Quality • Transition supply policy • Claims processing accuracy • Appeals/grievances • Clinical operations • Compliance program • Marketing/sales • Oversight of first tier and downstream entities (e.g., PBM)
Operational Audit	Assess policy/procedures, along with the accuracy and consistency of application in day-to-day operations Performing vendor oversight assessment and review of delegated functions and services	Accurate claims adjudication according to the plan's specific benefit design and member eligibility files
Financial Audit	Assessing accuracy of financial statements, records, payments, and reimbursements in accordance with company policies and/or contracts using accounting techniques and/or transparent analytics for assessment	• Accurate administration of pharmaceutical rebate contracts and risk-sharing provisions • Appropriate claims billing and reimbursement rates for medication and related services according to pharmacy and provider contracts

SBG encourages plans toward best practices in coverage policies and administration that:

- Includes a strong backbone in scientific support
- Embeds both medical and practical considerations that address the needs of the patient supported with a well-written and transparent rationale
- Allows consistent administration by department staff

Investing the time and resources up front for developing best practice coverage policies will prevent unnecessary appeals and overturns down the road and utilize resources more efficiently and effectively.

CMS also expects plans to be proactively identifying areas of risk by way of self-audit using CMS audit guides and tools and demonstrating remediation steps if issues are identified.

SBG has had unique and extensive visibility into CMS audits and investigation protocols. Health plan size is no exception—both large and small plans need to similarly invest in the rigors of audit readiness. The current critical areas that CMS focuses on from an audit perspective are as follows:

- **Formulary and benefit administration:** Rejected claims review, transition supplies
- **Coverage determinations, appeals, and grievances:** Clinical decision-making, processing documentation, effectuation timeliness
- **Compliance program effectiveness:** Organizational structure, governance
- **Special Need Plans (SNP)—Model of Care (SNP-MOC):** Enrollment, health risk assessments, care planning, case management documentation

Proactive mock audits efficiently facilitate being fully prepared to meet CMS requirements. Mock audits not only mirror the approach, scope, intensity, and timeframes of a CMS audit, but also provide the plan with a true representation of the expectations and risks that may be identified with an actual CMS audit. Once risks are identified, plans have the opportunity to address and document their step-by-step corrective action planning

About Solid Benefit Guidance

Bill Resnick

Headquartered in Montvale, N.J., Solid Benefit Guidance (SBG) was founded more than eight years ago with the vision of providing health plans and state and local governments with the opportunity to work with a consulting partner who truly understood the inner workings of the pharmacy benefit management (PBM) industry.

Bill Resnick, our founder, understood from his time at Empire Blue Cross Blue Shield and at Medco that many purchasers of PBM services did not fully understand all of the pricing, contracting, and operational elements encompassed in their agreements. While many consulting firms existed in the market to provide consulting support, most lacked professionals with institutional knowledge of PBM contracting, PBM auditing, PBM underwriting, retail pharmacy network development, medication manufacturer rebate contracting, MAC management, and specialty pharmacy management. The solution was to create SBG, a company of insiders with hands-on experience in all of the financial, clinical, and service components of the PBM industry—a company that could give clients the edge they need when auditing, negotiating, and managing their PBM relationship.

SBG has seen tremendous success in our eight-year history. SBG has managed more than 40 million members and is considered one of the nation's most prestigious pharmacy benefit consultancy firms. Our success and industry reputation is based on our ability to provide clients with an unparalleled pharmacy benefit evaluation, actionable information and insight, clinical guidance, and a best-in-class service experience that sets us apart from the competition.

and remediation. Although noncompliance issues are disheartening, CMS is likelier to look more favorably upon a plan that identifies issues and risks and takes steps to identify root causes and remediate. In addition, with proactive remediation of issues and mitigation of risks identified through a mock audit, plans can save significant time and staffing resources and protect their revenue and competitive positioning.

Clinical Programs Assessment

Clinical programs that include formulary and utilization management strategies, such as prior authorization and step therapy, are universal among health plans to manage appropriate use of medications and medication spend. The main differentiator in successfully administering these strategies is the plan's capacity to go beyond standardized formulary and prior authorization screening just for U.S Food and Drug Administration (FDA) approved use(s).

While it's prudent to stand on FDA approval to make coverage decisions, SBG supports health plans in expanding beyond the FDA's approval to develop robust best practices in utilization management programs. This includes solutions for the prescriber pushback on limiting coverage for off-label use. To limit coverage decisions based on FDA-approved use is generally inadequate and does not address the day-to-day reality of coverage requests.

Example: Hepatitis C Treatments

A prime example is the recent introduction of Sovaldi® and Olysio®, which literally changed the landscape of hepatitis C treatment overnight. Within weeks of the drugs' introduction on the market, plans found the challenges of administering coverage decisions based solely on FDA approval status versus considerations fueled by updated, complex practice guidelines and evolving, but preliminary, science for hepatitis C treatment and management.

SBG encourages plans toward best practices in coverage policies and administration that:

- Includes a strong backbone in scientific support
- Embeds both medical and practical considerations that address the needs of the patient supported with a well-written and transparent rationale
- Allows consistent administration by department staff

Investing the time and resources up front for developing best practice coverage policies will prevent unnecessary appeals and overturns down the road and utilize resources more efficiently and effectively.

As with any clinical program implemented, there is an obvious need to know if interventions have truly made a difference in positive health outcomes. Outcomes reporting is often very elusive due to lack of standards and disagreement on how measure outcomes should be calculated and documented.

Measurements are generally limited to service and process activities (number of doctor faxes, number of phone calls made to patients, number of letters sent), without ties to meaningful measures of outcome (e.g., medication adherence or reduction of claims cost over time). Activity reporting for clinical programs serves certain purposes to establish the breadth of outreach being conducted, numbers targeted, and staffing resources needed. However, these reports sometimes cloud the focus of tracking meaningful and practical metrics for medication adherence, change in medication utilization, or cost, which will paint a better picture of how well a clinical program may be performing.

When outsourcing various clinical programs, plans need to assure service level, performance guarantees, outcome metrics, or leading (surrogate) indicators that have reasonable and understandable ties to health outcomes. Clinical program contracts are often missing these, which can make negotiating a challenge. SBG has extensive experience in structuring arrangements and contracts with outsourced vendors to drive meaningful, clinical outcomes.

Conclusion

While there are likely many other areas that health plans are engaged in and focused on for opportunities, we see the recurring themes of specialty medication benefits, auditing, and clinical programs development and assessment as top priorities for many plans. There is a strong desire by health plan pharmacy departments to raise the bar both operationally and clinically.

SBG encourages plans to consistently gain perspective and keep a pulse from outside industry resources to understand their options and industry best practices.

The Future of Star Ratings: Changes, Challenges, and Strategies

Steve Cutts, PharmD, AE-C, CDOE, Vice President, Clinical Programs, Magellan Rx Management; and Caitlin Rothermel

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With 2014 well under way, it's time to consider the 2015 landscape for the ever-evolving Centers for Medicare & Medicaid Services (CMS) Star Ratings program. The 5-Star system provides a single measurement of overall Medicare Advantage (MA) and Prescription Drug Plan (PDP) quality. Consumers can take these ratings into account when selecting MA/PDP plans, and Star Ratings are increasingly important for a plan's bottom line, with quality bonus payments (QBPs) for high performance playing a key role in recovering reduced Medicare reimbursements.[1]

In 2015, the stakes for 5-Star quality will be even higher. Following a 2012–2014 demonstration project (in which QBPs were awarded to plans with three or more stars), bonus payments will be awarded only to plans with four or more stars going forward.[2] CMS will also make Star Ratings data more transparent and readily accessible to consumers.[3]

Starting in 2015, MA/PDP plans with 5-Star scores will be in a unique position: They will be allowed to market to patients year-round. On the other hand, low-performing plans (those with fewer than three stars over the preceding three years, or fewer than two-and-a-half stars for any combination of Part C or D summary ratings over three consecutive years) will find it harder to stay in business. These plans will experience new marketing restrictions, including a "low-performance" icon on their registration page. CMS will also send letters to low-performing plan patients suggesting they transfer to another plan. Eventually, patient enrollment may be blocked and/or the low-performing plan terminated.[1,3-5]

Proposed Changes for 2015 and Beyond

Some important adjustments to the Star Ratings are in the works for 2015. One change implemented for 2014, but with ongoing ramifications, is the proposal by CMS to round the measure data and cut points used for Star Ratings to whole numbers (including Part D Patient Safety measures). This was put in place to prevent small decimal value differences from resulting in performance rating variations. Measures

Table 1 2015 Proposed Revised 4-Star Thresholds[5]

Measures	Revised 4-Star Threshold
Cardiovascular Care–Cholesterol Screening	≥ 87%
Controlling Blood Pressure	≥ 65%
Diabetes Treatment	MA-PDs ≥ 87%; PDPs ≥ 84%
Medication Adherence for Oral Diabetes Medications	MA-PDs ≥ 78%; PDPs ≥ 79%
Medication Adherence for Hypertension (RAS Antagonists)	MA-PDs ≥ 79%; PDPs ≥ 81%
Medication Adherence for Cholesterol (Statins)	MA-PDs ≥ 74%; PDPs ≥ 76%

that will be exceptions (i.e., those that will still use decimal point rounding) include Part C and D Health and Drug Plan Complaints and Quality Improvements, and Part D Appeals Auto-Forward. Similarly, to improve scoring, CMS has proposed calculating overall and summary Star Ratings using individual measure scores rather than the Star Rating average for each individual measure.[5]

CMS will not change 4-Star thresholds for measures that have updated methodologies in 2015. However, in cases where the approach used to calculate a measure remains unchanged, adjustments will be made to the 4-Star threshold. This approach is designed to ensure a higher level of quality attainment over time. Consistent with this, and in support of the Million Hearts™ Initiative, increases of approximately 2 percent are proposed for certain 4-Star thresholds related to cardiovascular care and medication adherence (see Table 1, above).[5]

Specific to type 2 diabetes, CMS has proposed the addition of two new drug categories to the Diabetes Medication Adherence Star Ratings category in 2015, incretin mimetic agents and meglitinides (for a total of six medications categories evaluated).[6]

It is important to note that a number of Display Measures introduced in 2014 that were initially proposed to become 2015 Star Ratings measures have been retained as Display Measures. These measures include pharmacotherapy management of chronic obstructive pulmonary disease (COPD) exacerbation; treatment for alcohol and other drug dependence; and medication management program completion rate for comprehensive medication reviews. As shown in Box 1 (page 31), one new measure will be added to the 2015 CMS Star Ratings.[7]

Substantial changes are in the works for 2016 as well. To account for the loss of plan-specific information when individual measure scores are aggregated to summary or overall measures, CMS is considering moving away altogether from the defined 4-Star threshold methodology to one that removes predetermined 4-Star measurement thresholds. More detail is available in the April 14, 2014, CMS Final Call letter.[7]

> It is important to recall that the Star Ratings system is also designed to motivate health organizations to achieve better patient outcomes.

Strategies to Improve Star Rankings and Patient Outcomes

Available data suggests that MA/PDP plans are streamlining their operations and investing in effective star improvement strategies. According to an analysis by Avalere Health, the number of MA/PDP plans decreased by 5 percent between 2013 and 2014 (from 2,564 to 2,429). During the same time, the proportion of plans ranked as "above average" (four stars or more) grew from 27 percent to 42 percent, while those ranked "below average" (two-and-a-half stars or less) fell from 11 percent to 1 percent.[8] However, in both 2013 and 2014, only 19

Box 1: Measure to Be Added to 2015 CMS Star Ratings[7]

Measure	Definition
Special Needs Plan (SNP) Care Management (Part C)	The percentage of eligible SNP enrollees who received a health risk assessment during the measurement year

plans received a 5-Star rating,[9] and 82 Part C and 110 Part D plans saw their scores fall.[3] This indicates that many groups are still struggling to make the transition from above average to excellent.

Although improving Star Ratings has an obvious financial incentive for payors, it is important to recall that the Star Ratings system is also designed to motivate health organizations to achieve better patient outcomes. The system is still relatively young, and it is difficult to conclude whether there is a direct correlation between high ratings and improved patient outcomes. Given this, strategies by health plans to improve their Star Ratings should also include goals to directly improve patient outcomes, rather than simply chase higher ratings.

One way that health plans can help bolster their Star Rating and feel more confident that patient outcomes are being positively affected is through effective Medication Therapy Management (MTM) programs. Although the comprehensive medication review measure will remain as a display measure, MTM programs can still influence other Star Measures. The high-risk medications measure, diabetes patients on an ACE inhibitor or an ARB, and the various medication adherence metrics (antidiabetics, antihypertensives, lipid-lowering agents) are all measures that can be directly influenced with an MTM-based strategy. Furthermore, CMS requires that Part D sponsors must establish an MTM program that ensures covered Part D drugs are used to optimize therapeutic outcomes through improved medication use. The mandate requires Part D enrollees who are likely to incur annual costs for covered Part D drugs that exceed a predetermined level to be targeted for MTM programs. By combining these requirements with Star Ratings metrics, health plans can efficiently satisfy their MTM requirement and increase their likelihood of receiving bonus reimbursements through improved Star Ratings. By proactively identifying MTM eligible patients who will most likely impact multiple Star Ratings metrics and training MTM pharmacists on

Table 2 MTM Best Practice Strategies

Plan	MTM Process
Excellus BCBS	Uses pharmacists to contact Medicare Advantage members who are taking multiple medications for chronic conditions within a week of being discharged from the hospital
HealthPartners	MTM program reaches out to Medicare Advantage, Medicaid, and commercial members with chronic conditions taking multiple medications; the program offers patients the option of meeting with pharmacists in person, via phone, or through video conferencing
Florida Blue	Launched a campaign in 2013 in which pharmacists analyze medical and pharmacy data for patients with multiple chronic conditions; reaches out to the physicians with the identified potential medication-related problems as well as recommendations for improvement
Independent Health	Utilizes patient-centered medical homes to advance their medication management; pharmacists travel to these groups and hold discussions with providers and patients, including Star Measure-related topics, such as diabetes patients taking an ACE inhibitor/ARB

Source: AHIP Center for Policy and Research. Innovations in medication therapy management. Effective practices for diabetes care and other chronic conditions. December 2013.

Table 3 — Five Steps to Improve Member Engagement

1. Align member interaction preferences with Star Ratings goals; provide patients with online access to scheduling, test results, and health records.
2. Coordinate care to avoid multiple, siloed interactions.
3. Educate patients on their disease state and take steps to increase their self-management skills.
4. Regularly measure campaign effectiveness so that ineffective strategies are readily identified.
5. Incorporate key messaging into customer interactions, and use customer service staff and other outreach to deliver messaging.

effective intervention strategies, health plans may be able to optimize outcomes and quality ratings without incurring greater expenses.

Many health plans have been highlighted for their MTM strategies, including Excellus BCBS, HealthPartners, Florida Blue, and Independent Health. See Table 2, page 31, for more detailed information on how these plans are using an MTM approach to improve their quality and patient outcomes.

Drilling further down, providing patients with comprehensive, holistic case management ensures that systems actually function as expected. MTM programs provide a great opportunity for payors to be more engaging with patients. Getting member services right has never been more important due to the Star Ratings structure. More than 25 percent of the overall Star Ratings is based on member assessment of healthcare providers and systems,[10] and thus member satisfaction should be a priority for payors. Table 3 (above) outlines some steps that plans with high Star Ratings have taken to recognize members and improve retention.[11,12]

The Challenge of Incorporating Providers

A high-performing provider network is also essential to improving Star Ratings. Physicians and other healthcare providers play critical roles in ensuring member satisfaction, treatment adherence, and adequate data collection. Every provider should know and understand their critical role in ensuring high Star Ratings performance.

Table 4 — Five Steps Providers Can Take to Improve Star Ratings

1. Encourage patients to obtain recommended preventive screenings.
2. Communicate clearly and thoroughly with patients by using open-ended questions and regularly asking, "Do you have any questions?"
3. Coordinate with administrative staff to create office practices that identify noncompliant patients at the time of their appointment.
4. Review the CAHPS (Consumer Assessment of Healthcare Providers and Systems) survey to identify opportunities for the greatest in-office impact.
5. Try to incorporate health outcomes survey questions into each visit.

However, the system's incentives are directly tied to health plan organizations and not to providers. This provides a challenge for health plans to motivate individual providers to actively support the efforts to improve Star Ratings. To help align the goals of providers with those of the health plan, incentive programs should be put in place by health plans to reward high-value, quality care. These incentive programs should be tailored to meet the specific needs of the health plan and focus on primary care. Furthermore, underperforming providers should be identified, especially in areas where the health plan is struggling the most (lowest-rated Star Measures). Table 4 (page 32) outlines some provider-level tips that can be implemented in a range of clinical settings.[12-14]

Additionally, health plans may benefit from associating Star Measure improvements with the CMS Physician Quality Reporting System (PQRS). PQRS provides financial incentives directly to providers, if these providers meet the criteria for satisfactory submission of quality measures. Several of these measures have at least some level of overlap with Star Measures, including in the areas of diabetes, rheumatoid arthritis, and osteoporosis. Educating providers of these financial incentives may help motivate them to be more responsive to requests from health plans aimed at improving Star Ratings.

Conclusion

Achieving high Star Ratings scores has never been more important to the bottom line of MA/PDP plans. It has been estimated that a health plan with 100,000 MA member contracts could gain up to $300 per member per year, or $30 million, by increasing its Star Ratings to four or more.[10] Put another way, a one-half-point Star Ratings increase has been calculated to be worth approximately $50 per member per month.[3]

The process of becoming a CMS Star Ratings success is an ongoing but rewarding journey. Successful plans not only improve care delivery and outcomes, but also develop analytical and documentation strategies that readily communicate these successes. With a more clustered approach to scoring likely to kick off in 2016, strategies that focus on coordinating multiple Star Ratings priorities are likely to be the most successful going forward.

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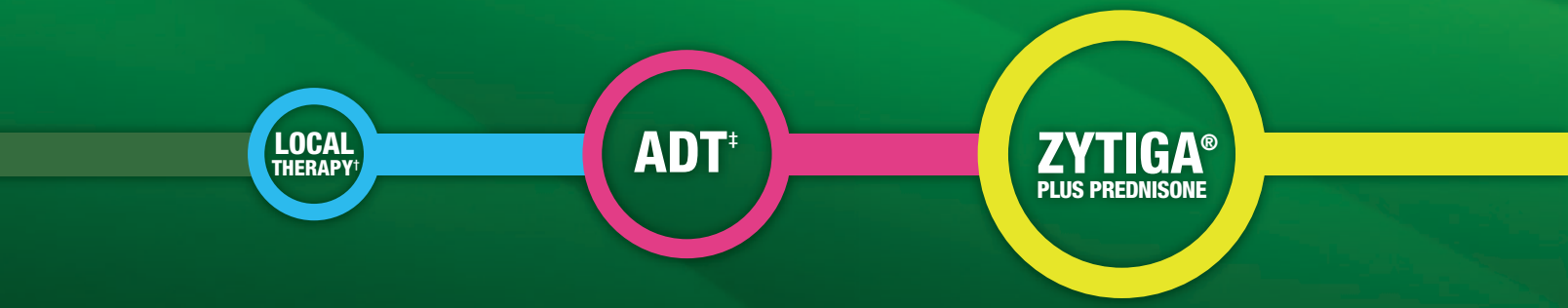

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IMPORTANT SAFETY INFORMATION

- **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.

once-daily

Zytiga®

(abiraterone acetate)

250 mg tablets

ZYTIGA® Next

5.2 Months

5.2-month difference in median overall survival vs placebo plus prednisone (median OS: 35.3 months vs 30.1 months, respectively)[§]

Hazard ratio (HR) = 0.792; 95% CI: 0.655, 0.956; *P* = 0.0151; prespecified value for statistical significance not reached.

57% Reduction

57% reduction in risk of radiographic progression or death vs placebo plus prednisone (median rPFS not reached vs 8.28 months, respectively)[§]

HR = 0.425; 95% CI: 0.347, 0.522; *P* < 0.0001.

Significantly increased median time to chemotherapy vs placebo plus prednisone (25.2 months vs 16.8 months, respectively)[‖]

HR = 0.580; 95% CI: 0.487, 0.691; *P* < 0.0001.

Significantly increased median time to opiate use for prostate cancer pain vs placebo plus prednisone (not reached vs 23.7 months, respectively)[‖]

HR = 0.686; 95% CI: 0.566, 0.833; *P* = 0.0001.

- **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).

K08Z12176

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

†Local therapy = radiation and/or surgery.

‡For many patients with mCRPC, gonadotropin-releasing hormone (GnRH) agonist therapy typically continues throughout the disease course, and is used concomitantly with other mCRPC treatments, including ZYTIGA®. This illustration is not intended to suggest that ZYTIGA® is the only treatment option following androgen-deprivation therapy (ADT).

[§]Primary endpoint.

[‖]Secondary endpoint.

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

Janssen Biotech, Inc.

3/13 K08Z13049

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

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[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

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janssen

Achieving Quality Improvement in Diabetes:
Impact of Antidiabetic Regimens on Clinical and Financial Outcomes

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Diabetes is a growing epidemic that is associated with a significant amount of healthcare expenditures. The World Health Organization (WHO) estimates the number of diabetics to be in the hundreds of millions and growing.[1,2] In the United States, diabetes-related spending is on the rise. The American Diabetes Association (ADA) conducted estimates of annual expenditures in 2007 and again in 2012. The total annual cost has risen 41 percent from $174 billion in 2007 to $245 billion in 2012.[3] As the number of insured Americans is increasing, the financial burden this patient population places on the healthcare system is only expected to rise. With this ever-increasing burden, it is crucial to ensure spending is optimized to produce favorable clinical outcomes in diabetic patients.

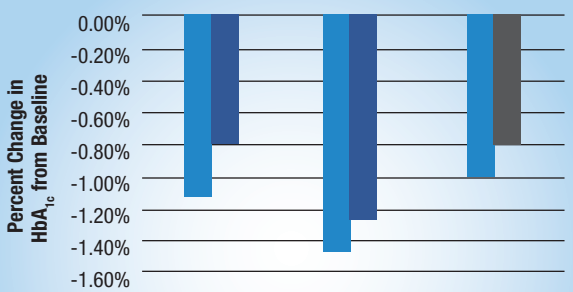
Treatment of type 2 diabetes is usually multifaceted and is aimed at reducing the significant morbidity and mortality associated with the disease state. It is widely known that tight glycemic control in diabetic patients can help improve overall outcomes, and different approaches have been extensively studied. Studies have shown that there is a benefit of aggressive treatment strategies compared to conventional treatment.[4] The ADA recommends a targeted glycosylated hemoglobin A1C level (HbA_{1c}) of less than 7 percent, which equates to effective chronic glycemic control over at least a three-month period.[5] With many diabetics, attaining this goal is not an easy task. Many patients require multiple therapies to reach desired results. This has spurred the development of numerous pharmacologic therapies with different targets and mechanisms of action.

One such target of therapy is modulation of incretin activity. Incretins are gastrointestinal hormones that regulate gut motility, gastric acid secretion, gallbladder contraction, nutrient absorption, and control of glucose-dependent pancreatic enzyme secretion. Successful modulation of incretins predominantly results in improved glycemic control and weight loss. Currently there are two classes of medication that employ incretin modulation. The first class includes degradation-resistant glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 is responsible for stimulat-

ing insulin and suppressing glucagon, as well as delaying gastric emptying and reducing appetite and food intake. The main drugs in this class are liraglutide (Victoza®, Novo Nordisk), exenatide (Byetta® and Bydureon®, AstraZeneca), and albiglutide (Tanzeum™, GlazoSmithKline), recently approved by the U.S. Food and Drug Administration (FDA). The second class includes inhibitors of dipeptidyl peptidase-4 (DPP-4), which is a protease that degrades GLP-1 and other incretins. There are various drugs in this class including sitagliptin, saxagliptin, alogliptin, and linagliptin. Both classes provide reduction in fasting and post-prandial glucose concentrations, and thus reductions in HbA_{1c}. GLP-1 agonists are associated with significant weight loss, whereas DPP-4 inhibitors tend to be more weight neutral.[6,7] In comparison, clinical data suggests that GLP-1 agonists provide more robust reductions in HbA_{1c} levels than DPP-4 inhibitors.

The mainstay of treatment for type 2 diabetes involves first-line treatment with metformin.[5] While monotherapy with metformin can be effective for some patients, depending on individual HbA_{1c} levels, it may not be enough to get a patient to the ADA's goal of less than 7 percent. In this case, there is a myriad of add-on treatment options before initiation of insulin therapy is required. The goal should be to preserve the patient's beta-cell function (a key measure in the progression of diabetes) for as long as possible before initiating insulin. While no current therapy durably improves beta-cell function after discontinuation, GLP-1 agonists and DPP-4 inhibitors offer an advantage over other classes, such as thiazolidinediones, sulphonylureas, and glinides, in terms of improving beta-cell function during treatment.[8-10]

Figure 1: Change in HbA_{1c} in GLP-1 Head-to-Head Trials[26-28]



	Lead-6	Duration-6	Harmony 7
Liraglutide	-1.12%	-1.48%	-0.99%
Exenatide	-0.79%	-1.28%	
Albiglutide			-0.78%

> Targeted utilization of GLP-1 agonists can have many benefits in the managed care realm. When it comes to getting patients to HbA_{1c} goals, these agents have been shown to be highly effective in those who are failing metformin or other oral antidiabetic therapy.

There is a growing amount of evidence supporting the use of newer agents. Many studies have been conducted comparing GLP-1 agonists and DPP-4 inhibitors to other second-line treatments. Generally, these newer agents tend to be more effective and carry fewer side effects than some of the other classes of drugs.[11] There is a much lower risk of hypoglycemia than with sulphonylureas; they carry no adverse cardiac events that thiazolidinediones have demonstrated, and they have no associated liver toxicity that the glinides carry.[12,13] When choosing add-on therapy to metformin, it is important to get the patient to his or her HbA_{1c} goal; that is, the most important focus is efficacy. GLP-1 agonists were able to lower patients' fasting plasma glucose and post-prandial glucose better than glimepiride, rosiglitazone, or insulin glargine, as seen in the LEAD trials conducted with liraglutide.[14-16]

In addition, there have been several trials comparing GLP-1 agonists to DPP-4 inhibitors that explore the relative HbA_{1c} reduction potential of the two antidiabetic classes. In the DURATION-2 trial, patients using exenatide had significantly lower HbA_{1c} levels than patients taking sitagliptin or pioglitazone, when taken with metformin.[17] There were similar results in the LIRA-DPP-4 trial comparing liraglutide to sitagliptin, in combination with metformin, where significantly more patients in the

liraglutide treatment arm reached their HbA_{1c} goal of 7 percent or less.[18] This evidence suggests that the GLP-1 agonists may offer superior HbA_{1c}-lowering potential than the currently available DPP-IV inhibitors. However, it is also important from the payor perspective to understand the financial impact that these various products have on health plan expenditures. Currently, there are a few pharmacoeconomic evaluations worth noting.

The first evaluation is an analysis of the short-term cost effectiveness of liraglutide versus sitagliptin. This analysis used data from the LIRA-DPP-4 trials and therefore focused on patients who were failing metformin monotherapy. Rather than using a traditional cost-effectiveness evaluation model, such as cost per quality-adjusted life year gained, a novel approach was developed. The analysis was based on cost per patient achieving a composite endpoint, which was reaching an HbA_{1c} of less than 7 percent with no hypoglycemia and no weight gain.[19] This endpoint mirrored recommendations from the ADA and is more realistic for third-party payors with regards to the Centers for Medicare & Medicaid Services (CMS) Star Ratings in diabetes management. Evaluations were completed for 26 and 52 weeks for both 1.2 and 1.8 mg of liraglutide and 100 mg of sitagliptin. Metformin doses were assumed to be 1,500 mg per day; however, changing the dose or cost of metformin did not significantly affect the overall cost effectiveness. In all calculations performed, both doses of liraglutide were significantly more cost effective than sitagliptin. It is important to note than even when the upper and lower limits of the confidence interval were compared (that is plus or minus 20 percent in terms of acquisition costs and successfully reaching the composite endpoint), liraglutide was always found to be a more cost effective agent. Also worth noting is the fact that liraglutide has a higher initial acquisition cost (roughly $800 to $2,700 per patient per year, depending on the dose). However, this is based on average wholesale and does not take into account any available discounts.[19]

Another cost-effectiveness evaluation was conducted to reflect updated diabetes treatment guidelines that included GLP-1 agonists, DPP-4 inhibitors, and long-acting insulin as second-line therapy to metfor-

Table 1 Summary of Head-to-Head Clinical Trial Results Comparing GLP-1 Agonists[26-28]

	LEAD-6	DURATION-6	HARMONY 7
Funding Manufacturer	Novo Nordisk	Amylin and Eli Lilly	GlaxoSmithKline
Medications Studied	Liraglutide once-daily Exenatide twice-daily	Liraglutide once-daily Exenatide once-weekly	Liraglutide once-daily Albiglutide once-weekly
Duration	26 weeks	26 weeks	32 weeks
Baseline HbA_{1c}	8.2%	8.4%	8.2%
HbA_{1c}	Liraglutide: -1.12% Exenatide: -0.79%	Liraglutide: -1.48% Exenatide: -1.28%◊	Liraglutide: -0.99% Albiglutide: -0.78%◊
Weight Change	Liraglutide: -3.24 kg Exenatide: -2.87 kg	Liraglutide: -3.57 kg Exenatide: -2.68 kg	Liraglutide: -2.2 kg Albiglutide: -0.6 kg
Systolic Blood Pressure	Liraglutide: -2.51mmHg Exenatide: -2.00mmHg	Liraglutide: -3.45mmHg Exenatide: -2.48mmHg	Liraglutide: <1 mmHg Albiglutide: <1 mmHg
Injection Site Reactions	Liraglutide: 8.9% Exenatide: 9.1%	Liraglutide: 1%* Exenatide: 10%*	Liraglutide: 5.4% Albiglutide: 12.9%
GI Events	Liraglutide: 45.5% Exenatide: 42.7%	Liraglutide: 21%† Exenatide: 9%†	Liraglutide: 49.0% Albiglutide: 35.9%

*Figure represents rate of most prevalent injection site reaction (nodule), excludes other injection site reactions (pruritus, erythema).
†Figure represents rate of most prevalent GI adverse event (nausea), excludes other GI adverse events (diarrhea, vomiting).
◊Change in HbA_{1c} from baseline did not meet predetermined criteria for non-inferiority.

min.[20] Meta-analyses were performed on multiple trials using the outcomes of HbA_{1c} reduction, hypoglycemic episodes, weight reduction, adverse events, quality of life, and cost. Using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model for cost effectiveness, each drug class was analyzed. The results showed that GLP-1 agonists were expensive, but also more cost effective than long-acting insulin, especially in the setting of failed oral therapy. This highlights a potential strategy of cost optimization in patients who have failed or are failing oral therapy; by identifying these patients and initiating GLP-1 agonists before switching to insulin, costs are diminished and greater results are obtainable. Some limitations of this analysis include the fact that there was little long-term data to analyze with regards to newer therapies, and the fact that the analysis was carried out from 2009 to 2010, when some of the newer agents had much higher acquisition costs.[20]

In addition to the aforementioned studies, there are two prevalent real-world retrospective cost-effectiveness analyses. These analyses compared laboratory, medical, and pharmacy claims from two major insurance databases for liraglutide daily versus exenatide twice daily. The first study was a cohort that utilized data from the IMS Patient-Centric Integrated Data Warehouse. It analyzed diabetes-related costs during a six-month period for liraglutide daily versus exenatide twice daily. This study used a similar tactic to the aforementioned short-term cost-effectiveness of liraglutide study in that it conveyed data in terms of cost per patient successfully reaching his or her HbA_{1c} goal. This is an excellent supplement for the fact that it supports the findings from the LIRA-DPP-4 analysis with real-world application. Although diabetes-related pharmacy costs were significantly higher with liraglutide, by about $250 over the six-month period, more patients reached their HbA_{1c} goal of less than 7 percent. This translated to a much lower per-patient cost of achieving goal when compared to exenatide.[21]

The second real-world cost-effectiveness analysis compared glycemic control, total diabetes-related healthcare costs, and time to medication discontinuation between liraglutide daily and exenatide twice daily. The data was taken from Optum Research Database, and the cohorts were randomized for various baseline characteristics. The analysis showed that exenatide treatment was associated with a significantly lower odds ratio of attaining glycemic control, defined as HbA_{1c} less than 7 percent. This translated to 51.7 percent versus 43.3 percent of patients meeting HbA_{1c} goal for liraglutide versus exenatide, respectively. Similarly, the analysis of time to medication discontinuation suggested that patients initiated on exenatide were greater than 2.2 times more likely to discontinue, versus liraglutide. Nevertheless, liraglutide treatment was associated with significantly higher diabetes-related total costs, which the authors attributed to a higher baseline diabetes complications severity index (DCSI) and higher out-of-pocket pharmacy costs for the index medication.[22]

With supposition of superior clinical efficacy and cost-effectiveness, GLP-1 agonists are promising with regards to treating type 2 diabetics who have failed oral therapy. When selecting which GLP-1 agonist to initiate, there is conclusive clinical evidence, in addition to the aforementioned cost-effectiveness studies, to offer guidance. Currently, there are four available formulations of three different agents: a twice-daily subcutaneous exenatide (Byetta®), a once-weekly subcutaneous exenatide (Bydureon®), a once-daily subcutaneous liraglutide (Victoza®), and a once-weekly subcutaneous albiglutide.[23-25] Several head-to-head trials have been conducted comparing the safety and efficacy of these various GLP-1 agonists in patients with type 2 diabetes (see Table 1, page 41).

With this wealth of clinical evidence and analyses, there are some important implications with regards to managed care. With healthcare reform, there is an ever increasing incentive to improve the quality of care delivered to patients. With such a large and growing prevalence of diabetes in the United States, the management of this disease state is an enormous target for improving outcomes. Managed care organizations have an opportunity for implementing improvement initiatives that can be fiscally worthwhile by optimizing therapeutic options, reducing overall healthcare utilization, and producing superior outcomes for patients with type 2 diabetes. Furthermore, in addition to heightening financial gains and reducing waste, a managed care organization's members will benefit from reduced morbidity and increased quality of life.

Targeted utilization of GLP-1 agonists can have many benefits in the managed care realm. When it comes to getting patients to HbA_{1c} goal, these agents have been shown to be highly effective in those who are failing metformin or other oral antidiabetic therapy.

Managed care organizations could implement therapeutic optimization programs that target patient populations who are using multiple oral antidiabetics and remain above their HbA_{1c} goals and recommend more efficient options. Another targeted strategy could involve identifying those who are on metformin monotherapy, and remain above goal, and recommending the most cost-effective and clinically appropriate therapies as preferred second-line options.

With all of this in mind, and in the era of healthcare reform, managed care organizations need to evaluate new strategies to improve diabetes-related quality metrics, specifically the CMS Star Ratings. Tight glycemic control, based on HbA_{1c}, is a difficult metric to improve upon and requires patient, provider, and payor alignment to ensure success. Most importantly, helping patients achieve their diabetes-related goals will inherently increase the quality of care delivered to patients with diabetes, increase quality of life, and decrease morbidity, while theoretically reducing long-term healthcare expenditures.

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0813-00017530-1

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 with hypersensitivity to Levemir® or any of its excipients.

Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision.

Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur.

Hypoglycemia is the most common adverse reaction of insulin therapy and may be life threatening. When a GLP-1 receptor agonist is used in combination with Levemir®, the Levemir® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia.

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®.

Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.

Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Levemir®.

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

Needles and Levemir® FlexPen® should never be shared.

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

The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia.

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

For pregnant women with type 1 diabetes:

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

For children and adolescents:

- Approved for use in members 2 years of age and older with type 1 diabetes[1,a]
- In children 2-5 years of age with type 1 diabetes, greater FPG reduction and fewer mild, moderate, and severe hypoglycemic events were seen than with NPH insulin[3,a]

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

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

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

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

Levemir® FlexPen®
insulin detemir (rDNA origin) injection

September 2013

CML Practice Guideline Update and FAQ

The treatment of chronic myeloid leukemia (CML) was revolutionized with the introduction of the tyrosine kinase inhibitor (TKI) drug class. Second generation TKIs, such as dasatinib and nilotinib, have further advanced treatment with more potent inhibitory activity and fewer side effects. However, drug resistance, underutilization of appropriate response monitoring, and wasted healthcare resources still pose challenges to the treatment of CML.

The treatment goals of TKI therapy include achieving a complete cytogenetic response within the first year and, eventually, a major molecular response, which signifies that the disease is under control. The standard protocol for monitoring response to treatment includes molecular studies conducted by quantitative polymerase chain reaction (qPCR), cytogenetic studies of the bone marrow, and fluorescent in situ hybridization (FISH). Cytogenetic studies have historically been the gold standard for evaluating response to TKI therapy. However, since most patients achieve complete cytogenetic responses with modern therapy, there is a need for additional testing to evaluate molecular response.

qPCR is used to identify a major molecular response or a complete molecular response and offers several advantages over cytogenetic studies. qPCR tests have the ability to measure leukemia cells that are too small to be detected with cytogenetic testing. In addition, qPCR tests quantify the amount of disease and have a greater sensitivity compared to cytogenetic studies. Evaluating molecular response is correlated with improved outcomes. Clinical data has shown that patients who achieved complete molecular response had better event-free and failure-free survivals than those with complete cytogenetic response irrespective of major molecular response status.[1] Thus, many specialists today use molecular studies in lieu of cytogenetic analysis to monitor response.

Recent studies have revealed resistance to imatinib to be present in up to 30 percent of instances. Point mutations of the BCR-ABL gene are the most common cause of TKI resistance and can be identified on blood or marrow specimens via mutational studies. Patients who have developed mutations are at higher risk for clinical disease progression. As each TKI has varying degrees of effectiveness against specific mutations, mutational studies can help guide therapy decisions by helping providers utilize the most cost effective salvage TKI based on each patient's unique clinical status.

National Comprehensive Cancer Network (NCCN) guidelines currently recommend that a qPCR should be conducted routinely at three, six,

12, and 18 months after treatment is initiated, followed by a mutational analysis if resistance is detected. Despite the availability of these monitoring tools and guideline recommendations, both tests are often underutilized. Many physicians are not appropriately monitoring response to therapy or are not modifying therapy based on response. One study reported that 69 percent of patients did not receive any molecular monitoring after initiating TKI therapy, and 83 percent of patients did not receive cytogenetic testing at the recommended three-month point.[1] Monitoring for both cytogenetic and molecular response was associated with a significantly higher overall survival rate at four years.

The frequency of qPCR conducted and the associated reduction in medical costs has also been investigated. Patients who underwent three to four qPCR tests during the first year of therapy incurred 44 percent fewer inpatient admissions than patients who did not undergo molecular monitoring. Adjusted all-cause inpatient cost per patient was significantly lower ($5,663 per 12 months) for the three-to-four-test group compared to patients who did not undergo any qPCR monitoring.

It is important to educate providers regarding appropriate guideline recommendations and emphasize the need and benefit for testing in this patient population. When patients do not respond to therapy as revealed through response monitoring, adherence and mutation assessments should be conducted. The most appropriate second, third, or fourth-line agent from a clinical and cost perspective should be chosen based on results of these mutation tests.

The second-generation TKIs are more potent and have often been reserved for patients who are resistant or intolerant to imatinib therapy. However, recent data indicates that second-generation TKIs as initial therapy offer intermediate-high-risk patients clinical and economic benefits.[2] As single-arm phase II studies first suggested, phase III randomized trials have found dasatinib and nilotinib to be superior to imatinib by inducing faster and higher rates of complete cytogenetic responses and molecular responses.[3-5] These results may ultimately translate into better outcomes. This data encouraged the U.S. Food and Drug Administration (FDA) to approve second-generation TKIs for the indication of patients with newly diagnosed CML in chronic phase. One of the possible explanations for the greater efficacy of the second-generation TKIs is their increased potency. Dasatinib, for example, is 325 times more potent than imatinib in inhibiting BCR-ABL activity due to an enhanced binding affinity. Furthermore, dasatinib is active against a number of imatinib-resistant BCR-ABL mutations (except for the T315I mutation).

The latest CML drug to be approved by the FDA, ponatinib, was introduced to the market in 2012. Ponatinib is unique in the fact that it has demonstrated efficacy against the T315I mutation, which the other currently available TKIs have not been able to achieve. Ponatinib was temporarily removed from the market in October 2013 due to concerns with high rates of cardiovascular events. Two months following this decision, however, the FDA allowed Ariad Pharmaceuticals to resume marketing and distribution of ponatinib (accompanied with prescribing information revisions and a REMS program). Per NCCN guidelines, ponatinib should be used only if the T315I mutation is identified or in a salvage setting after failing all other TKI therapies.

CML is a challenging disease state to manage from a clinical and economic perspective. However, by optimizing appropriate patient monitoring, health plans can ensure that their patients who develop a mutational resistance to imatinib can be identified and treated with the most appropriate second-line agents. An additional strategy to help physicians identify the root cause of treatment failure is to share patient-specific TKI adherence rates with the prescribing physicians. This will help the physician identify if the lack of response is due to the development of a mutation or simply lack of adherence to therapy.

Frequently Asked Questions

Why is response and mutation testing important?

Response testing helps the provider evaluate the effectiveness of the drug regimen and strengthen the accuracy of the prognosis. In addition, response monitoring plays an important role in the decision to conduct mutational analysis. Mutation studies help identify abnormalities in responders and demonstrate the need for treatment changes when necessary. Appropriate monitoring provides the patient with a greater chance for attaining a response and can help avoid waste.

What testing is done for monitoring response?

There are currently two tests that are considered standard in the initial workup for CML: bone marrow cytogenetic testing and quantitative reverse transcriptase polymerase chain reaction (qPCR). When obtaining bone marrow samples is unfeasible, FISH may be performed on the blood specimen.

What are the Sokal and Hasford scores?

The Sokal and Hasford scores are tools used to assess risk factors to determine the potential effectiveness of TKI therapy and to aid in selection of treatment. The Sokal score assigns patients into low-, intermediate-, or high-risk categories based on age, splenomegaly, platelet count, and percentage of

Table 1 — Oral Tyrosine Kinase Inhibitors Indicated for the Treatment of CML[2,7-12]

		Gleevec® (imatinib) Novartis – 1st Generation	Sprycel® (dasatinib) BM Squibb – 2nd Generation	Tasigna® (nilotinib) Novartis – 2nd Generation	Bosulif® (bosutinib) Pfizer – 2nd Generation	Iclusig® (ponatinib) Ariad – 3rd Generation
† Indications		1st line: CP, AP, BP	1st line: CP 2nd line: Any phase	1st line: CP 2nd line: CP or AP	2nd line: Any phase	T315I mutation: Any phase 3rd line: Any phase
‡Dosing Schedule	Initial	400 mg QD	100 mg QD	300 mg BID	*500 mg QD	45 mg QD
	Resistance	600 mg QD	140 mg QD	400 mg BID	*600 mg QD	45 mg QD
	Directions	Administered with a meal and large glass of water (reduces GI toxicity)	Administered without regard to meals	Must avoid food 2 hours before and 1 hour after administration	Should be taken with meal	Administered without regard to meals
Cost	WAC Per Day	$255.36	$306.14	**$310.60	$313.26	$345.00
	Per Year	$93,206	$111,742	$113,368	$114,340	$125,925

†FDA approved indications for use in Ph (+) CML adults

‡Recommended dosing for adults with Chronic Phase Ph (+) CML

*In the second-line setting, initial means after a TKI failure and resistance means that treatment response is less than optimal by 8 to 12 weeks of starting the second-line agent.

**For Tasigna: 150 mg x 4 pills = 300 mg BID

Table 2 — Management of Cytogenetic or Hematologic Resistance to TKIs[aa(6)]

Primary Treatment	Second-Line Therapy[bb,cc]	Third-Line Therapy[bb,cc]	Fourth-Line Therapy[bb,cc]
Imatinib →	Dasatinib[dd] → or Nilotinib[ee] → or Bosutinib[ff] →	Nilotinib[ee] or Bosutinib[ff] → Dasatinib[dd] or Bosutinib[ff] → Dasatinib[dd] or Nilotinib[ee] →	Clinical trial or Ponatinib[gg] or HSCT[cc] or Omacetaxine
Dasatinib →	Nilotinib[ee] or Bosutinib[ff] →	Clinical trial or Ponatinib[gg] or HSCT[cc] or Omacetaxine	
Nilotinib →	Dasatinib[dd] or Bosutinib[ff] →		

peripheral blasts. The Hasford score, used more commonly in Europe, adds to these prognostic factors the percentage of peripheral eosinophils and basophils. These assessments can help identify patients who may benefit from second-generation TKI treatment as their initial CML therapy rather than imatinib. Recent data indicates that second-generation TKIs as initial therapy offers intermediate-high-risk patients clinical and economic benefits. If patients are identified to have intermediate-high risk, a second-generation TKI may be the most effective treatment option as initial therapy.

How many patients with CML become resistant and in what time frame?

Approximately 30 percent of patients who initiate imatinib therapy will become resistant within one to two years.

What can a plan do to promote appropriate response testing?

Incorporating response testing into the utilization management process can help promote appropriate monitoring. Recertification of TKI therapy by the health plan should require qPCR to be conducted at a minimum of every six months.

What is the significance of the Standardized International Scale for PCR testing?

Quantitative monitoring of blood BCR-ABL1 markers may vary depending upon the laboratory setting. The International Scale (IS) ensures a standardization of the measurement of BCR-ABL1 facilitating inter-laboratory studies, patient portability, and the ability to properly define treatment response and treatment adjustment if needed.

Why was Iclusig® pulled off the market?

The FDA initiated an investigation, which revealed an increased frequency of blood clots and narrowing of blood vessels since the drug was approved in December 2012. Iclusig (ponatinib) was withdrawn from the market due to patients experiencing thromboembolic events in phase II clinical trials, including life-threatening myocardial infarction and severe vascular occlusion.

Why did the FDA decide to allow Iclusig back on the market?

Iclusig fills a niche in the market that other TKI products do not currently fill. Even though this product is accompanied with prescribing information revisions and a REMS program, it is the only product with demonstrated efficacy against the T351I mutation, which is the most common mutation and occurs in 13 percent to 16 percent of imatinib-resistant patients. The FDA decided that Iclusig should remain available to these patients who develop the T351I mutation and for patients who have tried and failed all other TKIs.

What is the appropriate patient profile for Iclusig?

Iclusig's return to the market was accompanied by a limited label indication and several warnings, including enrollment in a REMS program. Iclusig is indicated for the treatment of T315I mutation and treatment of all stages of CML in patients for whom other TKIs have failed or are not indicated.

Why is high-dose Gleevec® no longer recommended for resistant CML?

Under the current guidelines from the NCCN, the European Leukemia Network, and National Institute for Health and Clinical Excellence, high-dose 800 mg imatinib is not recommended in patients who have previously failed treatment with 400 mg imatinib. High-dose imatinib is associated with higher rates of dose interruption, decreased adherence, and overall discontinuation due to grade 3 or 4 adverse events. In addition, both the STAR and ENESTnd trials demonstrated that dasatinib and nilotinib produced better responses at two-year follow-up compared to high-dose imatinib. Thus, patients who require high-dose imatinib should be switched to second-generation TKIs when necessary.

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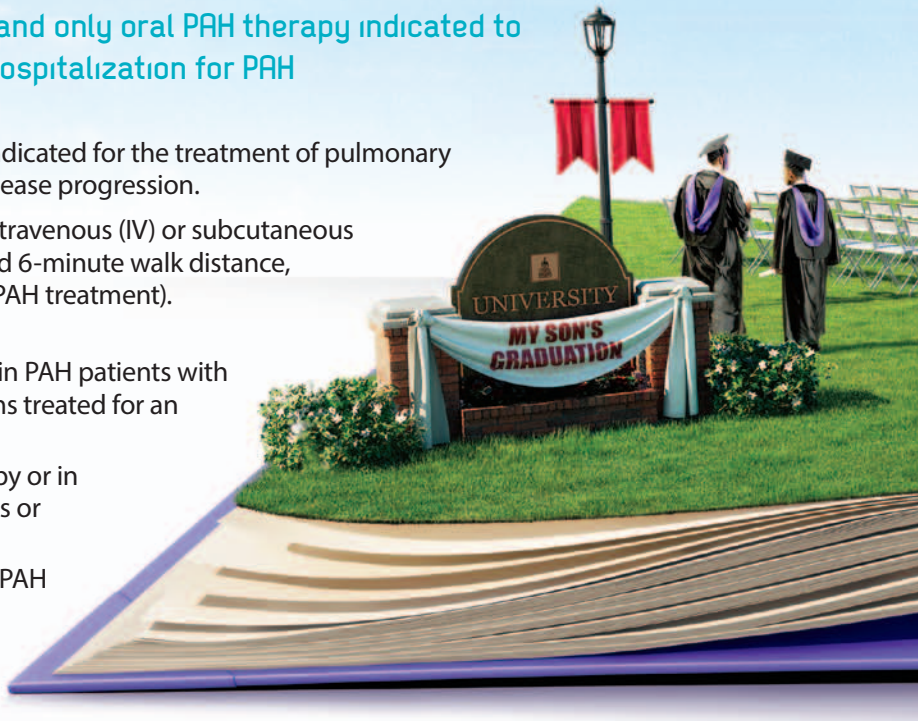
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH



OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS)**

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT

Patient dramatization

when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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macitentan tablets 10 mg

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Opsumit®
macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see *Warnings and Precautions (OPSUMIT REMS Program)*].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity),* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (Females and Males of Reproductive Potential)*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions (Clinical Trial Experience)*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242)	Placebo (N=249)
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see *Clinical Pharmacology (Pharmacokinetics)*].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

OPSUMIT® (macitentan)

Drug Interactions

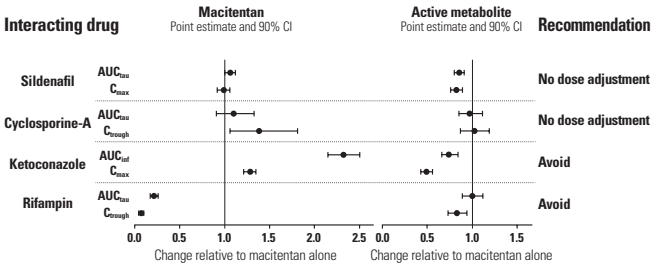
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see *Drug Interactions (Strong CYP3A4 Inhibitors)*].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.

ACTELION

PIPELINE TRENDS

NEW DRUG APPROVALS			
Drug	**Manufacturer**	**Approval Date**	**Indication**
Aveed™ (testosterone undecanoate) injection	Endo Pharmaceuticals	March 5, 2014	Long-acting androgen depot injection for the treatment of male hypogonadism
Xartemis™ XR (oxycodone/acetaminophen) tablet	Mallinckrodt	March 11, 2014	Extended-release analgesic and opioid agonist formulation for the management of moderate to severe acute pain
Otezla® (apremilast) tablet	Celgene	March 21, 2014	Phosphodiesterase 4 (PDE4) inhibitor indicated for the treatment of adults with active psoriatic arthritis
Alprolix™ (Coagulation Factor IX [recombinant]) injection	Biogen Idec	March 28, 2014	Clotting factor IX therapy indicated to prevent bleeding in patients with hemophilia B
Evzio™ (naloxone) injection	Kaleo Inc.	April 3, 2014	Opioid antagonist handheld auto-injector indicated for the emergency treatment of known or suspected opioid overdose
Tanzeum™ (albiglutide) injection	GlaxoSmithKline	April 15, 2014	Glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes
Cyramza™ (ramucirumab) injection	Eli Lilly	April 21, 2014	Human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated for the treatment of advanced gastric cancer
Sylvant™ (siltuximab) injection	Janssen	April 22, 2014	Interleukin-6 (IL-6) antagonist indicated for the treatment of patients with multicentric Castleman disease
Zykadia™ (ceritinib) capsule	Novartis	April 29, 2014	Kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer
Purixan™ (mercaptopurine) oral suspension	Nova Labs	April 28, 2014	Nucleoside metabolic inhibitor indicated for the treatment of patients with acute lymphoblastic leukemia
Incruse™ Ellipta® (umeclidinium) inhalation powder	GlaxoSmithKline	April 30, 2014	Anticholinergic bronchodilator indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD)
Zontivity™ (vorapaxar) tablet	Merck	May 8, 2014	Protease-activated receptor-1 antagonist for the prevention of cardiovascular events in high-risk patients
Entyvio™ (vedolizumab) injection	Takeda	May 20, 2014	Integrin receptor antagonist for the treatment of Crohn's disease and ulcerative colitis
Natesto™ (testosterone) intranasal gel	Trimel Pharmaceuticals	May 28, 2014	Intranasal gel testosterone for treatment of male hypogonadism
Vogelxo™ (testosterone) intranasal gel	Upsher-Smith	June 4, 2014	Androgen indicated for testosterone replacement in males with hypogonadism
Eloctate™ (antihemophilic factor) injection	Biogen	June 6, 2014	Recombinant, DNA-derived antihemophilic factor for treatment of patients with hemophilia A
Bunavail™ (buprenorphine and naloxone) buccal film	BioDelivery Sciences	June 6, 2014	Buccal opioid analgesic/opioid antagonist formulation for the maintenance treatment of opioid dependence

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

NEW FDA-APPROVED INDICATIONS

Drug	Approval Date	Indication
Imbruvica™ (ibrutinib)	February 12, 2014	Approved to treat patients with previously treated chronic lymphocytic leukemia
Eliquis® (apixaban)	March 13, 2014	Approved to reduce risk of blood clots following hip or knee replacement surgery
Xolair® (omalizumab)	March 21, 2014	Approved for chronic idiopathic urticaria
Pradaxa® (dabigatran etexilate)	April 7, 2014	Approved to reduce the risk of recurrence of deep vein thrombosis and pulmonary embolism

NEW FORMULATIONS AND DOSAGE FORMS

Drug	Approval Date	Advertised Advantage
Bydureon® (exenatide) injection	March 3, 2014	Prefilled pen approved for once-weekly treatment of adults with type 2 diabetes
Noxafil® (posaconazole) injection	March 13, 2014	IV formulation approved for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk
Nexium® (esomeprazole) capsule	March 28, 2014	Nexium 24 hour capsules approved to be available over-the-counter

NEW FIRST-TIME GENERIC DRUG APPROVALS

Drug	Approval Date
Raloxifene (Evista®) tablet	March 4, 2014
Oxybutynin (Oxytrol®) patch	March 4, 2014
Carbidopa (Lodosyn®) tablet	March 10, 2014
Atovaquone (Mepron®) oral suspension	March 18, 2014
Solifenacin (Vesicare®) tablet	April 2, 2014
Nevirapine (Viramune XR®) tablet	April 3, 2014
Omega-3-Acid (Lovaza®) capsule	April 7, 2014
Eszopiclone (Lunesta®) tablet	April 15, 2014
Atazanavir (Reyataz®) capsule	April 22, 2014
Metformin/Rosiglitazone (Avandamet®) tablet	May 7, 2014
Budesonide (Rhinocort Aqua®) nasal spray	May 12, 2014
Hydromorphone (Exalgo®) ER tablet	May 12, 2014
Atovaquone/Proguanil (Malarone®) tablet	May 27, 2014
Celecoxib (Celebrex®) capsule	May 30, 2014
Risedronate (Actonel®) tablet	June 10, 2014
Erlotinib (Tarceva®) tablet	June 11, 2014

CHRONIC HCV TREATMENT TRENDS

The treatment of HCV infection will change dramatically in 2014–2015 and onward. The advent of all oral, interferon-free combinations are expected to drive dramatic HCV market growth through 2021. These emerging direct-acting antivirals (DAAs) are being evaluated in all-oral, IFN-free regimens consisting of one to three DAAs in combinations with and without ribavirin. A report published by Decision Resources estimates the HCV market will grow from about $3 billion in 2011 to nearly $21 billion in 2018. It will then likely drop to $17 billion in 2021, owing to a decline in the size of the treatment-eligible population.

HCV TREATMENT PIPELINE

Drug Therapy	Manufacturer(s)	MOA	Genotype(s)	Development Phase
ABT-450/ritonavir + Ombitasvir + Dasabuvir	AbbVie	PI/NS5Ai	1	NDA filed April 2014
Daclatasvir + Asunaprevir	Bristol-Myers Squibb (BMS)	NS5Ai/PI	1b	NDA filed April 2014
Daclatasvir + Asunaprevir + BMS-791325	BMS	NS5Ai/PI/NNPI	1	Phase 3
Daclatasvir + Interferon Lambda	BMS	NS5Ai/Interferon	1,2,3,4	Phase 3
Daclatasvir + Peg-IFN	BMS	NS5Ai/Interferon	2,3	Phase 3
Daclatasvir + Sofosbuvir	BMS/Gilead	NS5Ai/NPI	All	Phase 3
Faldaprevir + Peg-IFN	Boehringer Ingelheim	PI/Interferon	1	PDUFA: Q4-2014
MK-5172 + MK-8742	Merck	PI/NS5Ai	1	Phase 3
Sofosbuvir + Ledipasvir	Gilead	NPI/NS5Ai	1	PDUFA: October 10, 2014

NPI: Nucleotide Polymerase Inhibitor; **NS5Ai:** NS5A Inhibitor; **PI:** 2nd Generation Protease Inhibitor; **NNPI:** Non-Nucleoside Polymerase Inhibitor

Raising Awareness of Medication Adherence Through Community Campaigns

The trend of poor medication adherence has been a concern within the healthcare industry for many years. Payors, PBMs, providers, employers, pharmacists, nurses, etc., all have a vital role in improving patients' adherence to their medications. The scope of the problem of non-adherence in the United States is staggering; poor adherence costs the healthcare system nearly $300 billion annually.[1] Seventy-five percent of healthcare costs are attributed to chronic diseases, and medication adherence amongst patients with chronic diseases is a critical component to optimize clinical and financial goals.[2] As treatment prices increase with the surge of specialty medications, the concern for adherence has grown stronger for payors.

There are numerous strategies that can be taken to address non-adherence. Healthcare professionals directly involved in patient care can be more active in discussing with their patients the importance of taking medications as directed. Understanding potential adherence barriers for patients and addressing these issues prior to the initiation of therapy can also be beneficial. Large organizations, including health plans and manufacturers, have developed adherence programs to help patients stay on track with their treatment. To reach patients on a larger scale, health organizations have also launched community campaigns to help raise awareness and educate patients on the importance of medication adherence.

In 2011, a national campaign effort, *Script Your Future*, was launched with grants received from the U.S. Food and Drug Administration (FDA).[3] The campaign provides tools and information for patients aimed at increasing awareness of medication adherence.[4] The campaign makes appearances at community events and partners with many large organizations, including government agencies, manufacturers, researchers, and other large health-related associations.

Regional health plans can also utilize the community campaign approach to increase awareness of the importance of medication adherence. Excellus BlueCross BlueShield, a regional health plan based in Rochester, N.Y., recently partnered with other upstate New York health groups to launch "TAD," short for "Take As Directed."[5] TAD is a superhero version of a pill bottle, dressed with a cape and a utility belt mirroring a daily pill organizer; TAD's belt buckle reads "Protect Your Health." The medication adherence superhero campaign is now featured on billboards, radio commercials, and print publications throughout upstate New York.

In addition to the various communication and publications associated with the adherence campaign, Excellus BCBS has also established a website to complement TAD (**excellusbcbs.com/takeasdirected**). The website features information about medication adherence and some of the common adherence barriers patients often face. These barriers include side effects, costs, convenience, forgetfulness, and attitude toward the necessity of the medication. A link is also provided for members to email a pharmacist with questions regarding any medication adherence concerns.

"Taking your medication as directed is one of the most important things you can do to improve your health," said Mona Chitre, PharmD, Vice President and Chief Pharmacy Officer, Excellus BCBS. "Yet many individuals fail to take their medication as they should. We took a unique approach to this campaign so that we could empower and arm community members with the tools they needed to take their medications as directed. The goal is to help individuals improve their health and quality of life and control rising healthcare costs."

A local survey was conducted to measure the initial impact of the TAD campaign on the local community.[6] The survey was conducted over two phases three months apart. The first phase of the survey found only 3 percent of the participants recalled some sort of messaging involving medication adherence. This number increased to 15 percent for the second phase of the survey, demonstrating that the campaign was penetrating into the community. Furthermore, the amount of participants familiar with the term "medication adherence" also increased, as did the amount of participants who could choose the correct meaning of medication adherence.

Community efforts to improve medication adherence can help individuals improve their health and save money. If an individual acquires the medication but does not take it appropriately and fails treatment, healthcare dollars are wasted and the health of the individual could deteriorate. The patient will continue to drive costs with disease-related complications that should have been eradicated with proper adherence to treatment.

In addition to the typical approaches to improving patient adherence at the individual level, raising awareness through community campaigns allows regional health plans to reach their members on a larger scale. As demonstrated by the Excellus BCBS TAD campaign, utilizing a creative advertisement-based campaign can increase patients understanding of medication adherence and its impact on health outcomes.

References

1. New England Health Institute. Thinking outside the pillbox: A system-wide approach to improving patient medication adherence for chronic disease. Accessed 10 June 2014 at **http://www.nehi.net/writable/publication_files/file/patient_adherence_onepager_2009.pdf**.
2. Centers for Disease Control and Prevention. Chronic diseases—The power to prevent, the call to control: At a glance 2009. Accessed 10 June 2014 at **http://www.cdc.gov/chronicdisease/resources/publications/aag/chronic.htm**.
3. Federal Register. Campaign to improve poor medication adherence. Accessed 10 June 2014 at **https://www.federalregister.gov/articles/2011/03/09/2011-5287/campaign-to-improve-poor-medication-adherence-u18**.
4. Script Your Future. Accessed 10 June 2014 at **http://www.scriptyourfuture.org/**.
5. Excellus BlueCross BlueShield. Campaign introduces new superhero to protect the health of local citizens. Accessed 10 June 2014 at **https://www.excellusbcbs.com/wps/portal/xl/our/news/newsreleases/corp**.
6. Data on file; provided by Excellus BlueCross BlueShield.

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

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

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; Angioedema and anaphylactic reactions; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

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

More detailed information is available upon request.

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

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

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

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

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

novo nordisk®

The change begins at **VictozaPro.com**.

VICTOZA®
liraglutide (rDNA origin) injection

Indications and Usage

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

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

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

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

Please see brief summary of Prescribing Information on adjacent page.

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