Spring 2014

The Evolving Prostate Cancer Landscape

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Management of Renal Cell Carcinoma

Magellan Rx Report

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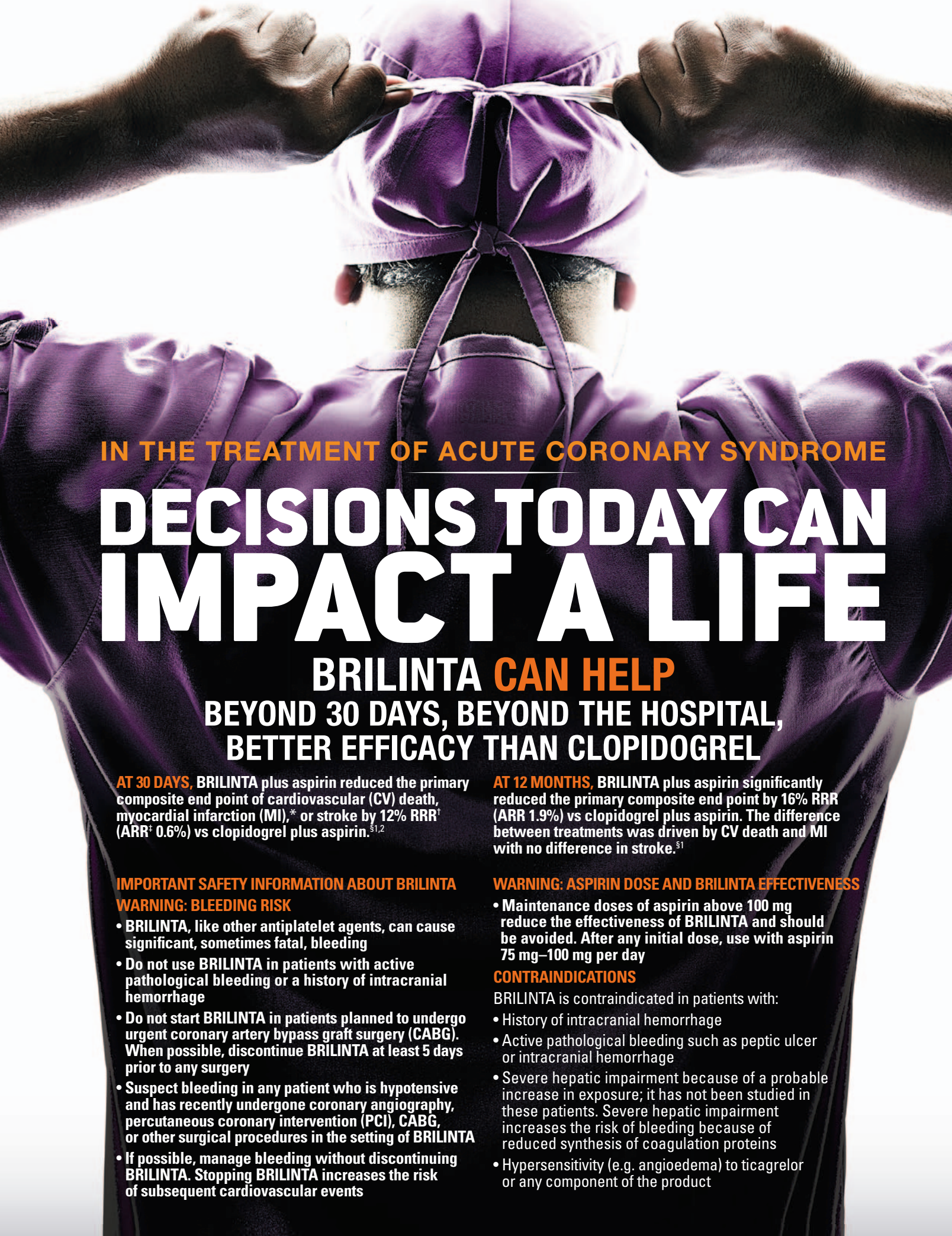


IN THE TREATMENT OF ACUTE CORONARY SYNDROME

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: 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**

WARNING: 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:

- History of intracranial hemorrhage
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- 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
- Hypersensitivity (e.g. 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 CV events in patients with acute coronary syndrome (ACS) (unstable angina [UA], non–ST-elevation MI [NSTEMI], or ST-elevation MI [STEMI]). BRILINTA has been shown to reduce the rate of a combined end point of CV death, MI, or stroke compared with 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.

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]

*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).

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

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: 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 surgical procedures in the setting of BRILINTA [see WARNINGS AND PRECAUTIONS].**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see WARNINGS AND PRECAUTIONS].**

WARNING: 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 75-100 mg per day [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*]

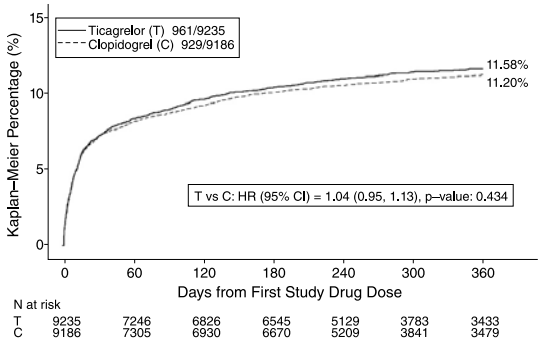
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety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

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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WELCOME

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Letter from the President

Susan Petrovas

Dear Managed Care Colleagues,

2014 will be a defining year for the healthcare industry. With the implementation of many aspects of the Affordable Care Act, specialty drug costs continuing to increase, and an even greater emphasis placed on quality of care, health plans throughout the country will have to reassess their previous management strategies in order to adapt to the current healthcare landscape and remain competitive and financially stable.

Susan Petrovas, RPh, President

We have entered an age where segmentation of healthcare benefits is no longer a sustainable management approach. With the costs of treating patients nearing unmanageable levels, inappropriate/duplicative resource consumption and expensive negative outcomes must be minimized. Formulary and utilization management controls are not enough to appropriately manage patients and resources in today's environment.

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

Health plans should focus their efforts on optimizing cost-effective treatment strategies, aligning medical and pharmacy benefits, and proactively supporting clinical initiatives designed to improve high-quality outcomes. This may require the development of new strategies to manage high-cost disease states (such as MS, RA, HCV, oncology, diabetes, hemophilia, etc.) to ensure that each dollar spent on therapy is enhancing the chances of achieving positive patient outcomes.

As always, CDMI offers our support to ensure our clients can optimize the value of care provided to their patients. Our company's core objective is to drive quality outcomes in both specialty and traditional disease states with strategies that can be customized based on plan-specific needs and patient populations. In addition to our medical and pharmacy benefit management services, CDMI offers a comprehensive approach to improving clinical and economic outcomes in high-cost disease states, including programs designed to improve adherence/persistency, coordination of care, and site-of-care optimization for our clients' beneficiaries. Each program is developed in tandem with key opinion leaders in their respective fields to ensure compliance with evidence-based best practices, feasibility of implementation, and ability to improve clinical and financial outcomes.

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

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

MANAGED CARE NEWSSTAND

Early RA Treatment May Improve Outcomes

Prompt and effective treatment for rheumatoid arthritis (RA) helps prevent future joint damage and disability. Canadian researchers based their findings on data from the Canadian Early Arthritis Cohort (CATCH). They studied patients with early RA who had symptoms for one year or less and classified them into two categories: those who achieved low disease activity by six months and those who did not. The researchers found that patients who achieved low disease activity by six months had much better functional abilities two years later, as measured by the health assessment questionnaire.

"We believe there is a window in which people have a much better chance of getting rheumatoid arthritis under good control, often with less intense therapy, and the window is within the first three months of developing joint inflammation," said Vivian Bykerk, MD, one of the researchers involved in the study.

This study demonstrates the importance of encouraging patients to receive early and appropriate treatment for RA to maximize their outcomes. Those who delay treatment, according to the researchers, may need more intensive treatment to control their disease.

Source: Akhavan P, et al. Reaching the target of low disease activity at 6 months predicts better long-term functional outcome in patients with early rheumatoid arthritis. Annual meeting of the American College of Rheumatology. Abstract. October 26-30, 2013.

Certain Drugs for Rheumatoid Arthritis May Reduce Heart Risk

Two groups of researchers have found that biologic medications that help ease symptoms of rheumatoid arthritis (RA) may also offer some protection for the heart. They reported their findings at the annual meeting of the American College of Rheumatology.

Swedish researchers found that certain tumor necrosis factor inhibitors (TNFi) modestly reduced the risk for acute coronary syndrome in patients with RA. As part of the study, researchers compared RA patients taking TNFi to RA patients not taking these drugs and the general population. They reported that the risk for angina and heart attacks was lower in RA patients taking anti-TNFs than those RA patients who had never taken these drugs.

In another study, researchers in the United Kingdom compared heart attack risk and severity in RA patients taking TNFi and those taking non-biologic drugs. They reported that the risk for heart attack was lower in those taking TNFi. However, the severity of heart attack was similar for patients taking either medication.

Both groups of researchers said the reduced cardiovascular risk could be the result of the medications or improved disease control.

Sources: Ljung L, et al. Tumour necrosis factor inhibitors and the risk of acute coronary syndrome in rheumatoid arthritis—a national cohort study. Annual meeting of the American College of Rheumatology. Abstract 804. October 26-30, 2013.

Low A, et al. Incidence and severity of myocardial infarction in subjects receiving anti-tumour necrosis factor drugs for rheumatoid arthritis: Results from linking the British Society For Rheumatology Biologics Register for rheumatoid arthritis and myocardial ischaemia national audit project. Annual meeting of the American College of Rheumatology. Abstract 2760. October 26-30, 2013.

Early HIV Treatment Improves Patients' Health and Helps Prevent Transmission

A new study has found that early treatment of patients recently infected with HIV with antiretroviral therapy (ART) is a cost-effective way to help these patients stay healthy and reduce the risk that they will transmit the disease to uninfected partners. Researchers used data from an international research collaborative called the HIV Prevention Trials Network to determine the cost-effectiveness of ART in South Africa and India, countries that have the highest HIV infection rates in the world.

The researchers found that early ART saved money in South Africa because it helped prevent costly opportunistic infections. While early treatment did not save money in India, it was still considered to be cost-effective. ART was considered cost-effective in both countries across patient lifetimes. There were fewer illnesses and deaths among infected patients and treatment reduced HIV transmission.

The researchers said that investing in HIV treatment in countries with limited resources could save millions of lives over the next decade.

Source: Walensky R, et al. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. *NEJM*. 2013;369(18):1715-1725.

Investigational Drug Combos Offer Hope for Patients with Hard-to-Treat Hepatitis C

Two phase 2 clinical studies that evaluated the safety and efficacy of all-oral combination therapies for patients infected with hepatitis C were recently published in the *New England Journal of Medicine*. Both studies have shown that high rates of sustained virologic response (SVR) are possible in the absence of interferon.

The first study evaluated the efficacy of combination therapy with once-daily, oral antiviral drugs daclatasvir (60 mg daily) and sofosbuvir (400 mg daily) for patients infected with HCV genotypes 1, 2, or 3. Patients were treated for 24 weeks with or without ribavirin. The study included both treatment-naïve patients and those who have failed previous triple-drug therapy with either telaprevir or boceprevir.

Among patients with HCV genotype 1, 98 percent of treatment-naïve and 98 percent of treatment-experienced patients demonstrated a SVR at 12 weeks after treatment completion. Patients with HCV genotypes 2 and 3 also demonstrated high rates of SVR (92 percent and 89 percent, respectively).

The second study evaluated an 8-, 12-, and 24-week all-oral, interferon-free treatment regimen in HCV genotype 1 patients who were treatment-naïve or had failed prior therapy. The study evaluated various dosage combinations of ABT-450, an NS3/4A-protease inhibitor, with ritonavir (ABT-450/r), combined with non-nucleoside NS5B polymerase inhibitor ABT-267, ABT-333, or both. SVR ranged from 83 percent to 100 percent across all treatment groups.

Sources: Sulkowski MS, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *NEJM*. 2014;370:211-221.

Kowdley KV, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *NEJM*. 2014;370:222-232.

More Couples Have Successful Pregnancies Using Donor Eggs for IVF

The use of donor eggs during in vitro fertilization (IVF) has increased significantly over the past decade. Researchers used the United States' National ART Surveillance System (NASS) to evaluate the use of donor eggs, as well as maternal and infant outcomes. Data from 93 percent of all fertility clinics in the United States from 2000 to 2010 were included.

The researchers found that the number of donor IVF cycles rose dramatically from nearly 11,000 to more than 18,000 during the study period. Good birth outcomes increased from more than 18 percent to more than 24 percent. And in 2010, more than 27 percent of cycles using fresh embryos had good outcomes. The researchers reported that good outcomes were associated with the transfer of embryo at day five and elective single-embryo transfers. Poor outcomes were associated with uterine or tubal infertility factors and non-Hispanic black recipients. The age of recipients did not affect outcomes.

This research suggests that the use of donor eggs may be an effective option for some couples who have a lower likelihood of delivering a healthy baby. The work identifies opportunities for further improvements in IVF outcomes.

Source: Kawwass J, et al. Trends and outcomes for donor oocyte cycles in the United States, 2000-2010. *JAMA*. 2013;310(22):2426-2434.

Radiation for Breast Cancer May Increase Heart Disease Risk

Breast cancer patients who undergo radiation therapy may have a slightly higher risk for heart disease, though the risk has declined over the past two decades. A study by radiologic researchers at Columbia University Medical Center found that breast cancer patients' risk for heart disease varies based on their underlying risk for heart disease.

The researchers say the average lifetime risk for serious heart disease from radiation exposure is less than 1 percent. The risk is higher in women already at high risk for heart disease. These findings apply to women with cancer in the left breast. Radiation in this area is closer to the heart.

The researchers say women should not avoid radiation therapy because the risk of future heart disease is low. They suggest that women can lower their risk by taking steps to reduce their overall chances of developing heart disease.

Source: Brenner D, et al. Risk and risk reduction of major coronary events associated with contemporary breast radiotherapy. *JAMA Intern Med*. 2014;174(1):158-160.

Xtandi (enzalutamide) capsules

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION
The following is a brief summary: please see the package insert for full prescribing information.

---------- INDICATIONS AND USAGE ----------
XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

---------- CONTRAINDICATIONS ----------
Pregnancy
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. 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 ----------
Seizure
In the randomized clinical trial, 7 of 800 (0.9%) patients treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizures.
The safety of XTANDI in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold.
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 ----------
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 practice.
In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel, patients received XTANDI 160 mg orally once daily (N = 800) or placebo (N = 399). The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. All adverse events and laboratory abnormalities were graded using NCI CTCAE version 4.
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 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in the randomized clinical trial that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[a]	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0

(continued) **Table 1. Adverse Reactions in the Randomized Trial**

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[b]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[c]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[d]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[e]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a Includes asthenia and fatigue.
b Includes dizziness and vertigo.
c Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
d Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
e Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Laboratory Abnormalities
In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on XTANDI (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on XTANDI and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on XTANDI (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on XTANDI and 2% of patients on placebo.
Infections
In the randomized clinical trial, 1.0% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related serious adverse events were reported in approximately 6% of the patients on both treatment arms.
Falls and Fall-related Injuries
In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with XTANDI compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.
Hallucinations
In the randomized clinical trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

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.
- Inform patients that XTANDI may be harmful to a developing fetus. Patients should also be informed that they should use a condom if having sex with a pregnant woman. A condom and another effective method of birth control should be used if the patient is having sex with a woman of child-bearing potential. These measures are required during and for three months after treatment with XTANDI.

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716
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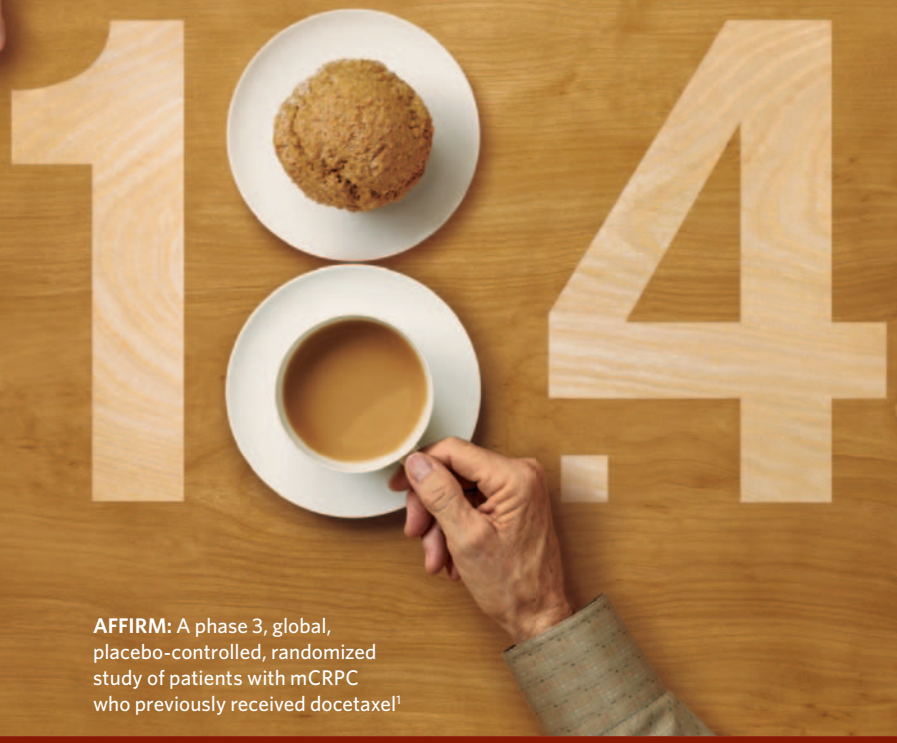
MEDIVATION

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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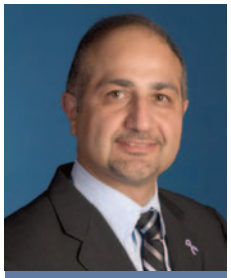
Pulmonary Arterial Hypertension and Managed Care

Roham T. Zamanian, MD, FCCP, Director, Adult Pulmonary Hypertension Clinical Service, Vera Moulton Wall Center for Pulmonary Vascular Disease, Assistant Professor of Medicine, Stanford University School of Medicine; and Daria I. Grisanzio, PharmD



Roham T. Zamanian, MD, FCCP

Pulmonary arterial hypertension (PAH), a form of pulmonary hypertension (PH), is an often progressive disorder developing due to restricted pulmonary arterial circulation, which results in increased pulmonary vascular resistance, right ventricular dysfunction, and may lead to right heart failure and death.[1-4] Although the pathogenesis is not fully known and is also quite diverse and complex, the proposed mechanisms include both environmental and genetic factors, with dysfunction occurring via prostacyclin, endothelin, and nitric oxide (NO) pathways.[1,2,4] Prevalence of PAH is estimated at 15 to 26 per million people (approximately 130,000 to 260,000 worldwide), with an annual incidence of approximately 1.1 to 7.6 per million people.[2-4]

PAH is categorized by the World Health Organization (WHO) classification for PH; PAH is Group 1 under this system, comprising five subcategories and a separate, yet related, subgroup (Group 1) (Table 1, page 14).[2,5] The most common symptoms of PAH include edema, fatigue, chest pain, exercise intolerance, syncope, and dyspnea on exertion, although early stages are typically asymptomatic.[3,4,6] The impact on patient quality of life (QOL) and health-related QOL (HRQOL) can be significant and affect mental, physical, and social domains.[7] Diagnosis often occurs during later, more advanced, stages of disease.[3,4,6]

Overall, the prognosis in patients with PAH is poor and varies based on disease type and associated comorbidities, with five-year survival in untreated patients ranging from 34 to 50 percent.[3,6,8] Recently, in a single-center prospective study of 109 patients with idiopathic PAH (IPAH), Nickel et al demonstrated that improvements or deteriorations in functional class over time were significant predictors of survival.[26] In addition, patients with PAH associated with congenital heart disease (CHD-APAH) tend to live longer than those with connective tissue disease-associated PAH (CTD-APAH). Risk stratifying patients has been recommended based on disease severity, rate of deterioration, and underlying cause.[27]

Between 1995 and 2002 in the United States, there were 1.9 million hospitalizations and 117,000 deaths attributed to PAH. The annual cost of pharmacologic treatment is approximately $18,000 to $244,000 (Table 2, page 16).[8] The cost of treatment also includes the use of specialized delivery

systems and monitoring considerations along with the need for experienced medical care.[2,7,9] While the cost of initiating PAH-targeted treatment is expensive, registries such as REVEAL and FRENCH demonstrate improvement in outcomes.[28,29] A meta-analysis by Galie et al has also shown that there is a 43 percent risk reduction with therapies for PAH, which may also suggest a reduction in other healthcare costs, such as inpatient and outpatient services.[3,6,30]

ACCF/AHA Guidelines

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have developed expert consensus guidelines for PAH, which are periodically reviewed and updated. The most recent update to the guidelines was in 2009.[2] Diagnosis of PAH requires a number of pivotal and contingent tests, including patient history, physical exam, radiographic assessments, echocardiographic studies, pulmonary function tests, and functional tests (e.g., six-minute walk test [6MWT]). Specific criteria must be met in order to definitely diagnose PAH.[2]

As there is significant variation in PAH presentation between patients, treatment should be individualized. Treatment is recommended based on PAH subcategory, prognosis, severity of disease, symptoms, comorbidities, disease function (by WHO or New York Heart Association [NYHA] grade), treatment goals, and medication-related considerations (e.g., route of administration, adverse event profile). Conventional therapies are recommended for the treatment of comorbidities and may potentially include diuretics, anticoagulants (IPAH only), oxygen, and occasionally digoxin. In fact, a recent study called COMPERA showed a significantly better three-year survival (p=0.006) in patients with IPAH on anticoagulation compared with patients who never received anticoagulation.[38] Additional non-pharmacologic measures, such as diet, exercise, and physical rehabilitation, are also recommended, along with appropriate vaccination.[36] It is also recommended that female patients avoid pregnancy due to the significant hemodynamic changes that occur. Patients—including those with IPAH—who are candidates for long-term calcium channel blocker (CCB) therapy should undergo acute vasodilator testing to determine if CCB therapy should be initiated; response to CCBs in non-IPAH patients is low, and acute vasodilator testing must be individualized in these patients. If CCBs are initiated, patients should be monitored closely for safety and efficacy.[2]

Patients who are not candidates for CCBs or who have a negative acute vasodilator test should be categorized as low- or high-risk based on clinical assessment (i.e., evidence of right ventricular failure, progression of symptoms, WHO class, 6MWT, cardiopulmonary exercise testing, echocardiography, hemodynamics, and brain natriuretic peptide [BNP]). Low-risk patients should be started on an oral endothelin receptor antagonist (ERA) or phosphodiesterase-type 5 inhibitor (PDE5-I) as first-line treatment; treatment should be individualized and alternative treatment with non-oral prostacyclin may be considered. Second-line treatment for low-risk patients includes non-oral prostacyclins, oral ERA, or PDE5-I (if not given first line) or consideration of combination therapy. Investigational agents should be considered third-line. High-risk patients should be started first-line on continuous intravenous prostacyclin therapy, with treatment individualized for the patient and including options of oral ERA or PDE5-I and non-infused prostacyclins. Second-line treatment options include combination therapy or investigational agents. In both low- and high-risk patients who have progressed despite optimal treatment,

Table 1 World Health Organization 2009 Updated Pulmonary Arterial Hypertension Classification[5]

1	**Pulmonary arterial hypertension**
1.1	Idiopathic
1.2	**Heritable**
1.2.1	BMPR2
1.2.2	ALK1, endoglin (± hereditary hemorrhagic telangiectasia)
1.2.3	Unknown
1.3	**Drug and toxin induced**
1.4	**Associated with**
1.4.1	Connective tissue diseases
1.4.2	HIV
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.4.6	Chronic hemolytic anemia
1.5	**Persistent pulmonary hypertension (in newborns)**
1'	**PVOD and/or PCH**

Key: **ALK1**=activin receptor-like kinase type 1; **BMPR2**=bone morphogenetic protein receptor type 2 gene; **HIV**=human immunodeficiency virus; **PCH**=pulmonary capillary hemangiomatosis; **PVOD**=pulmonary veno-occlusive disease

surgery (i.e., lung transplant or atrial septostomy) should also be considered.[2]

Patient Monitoring

Patient follow-up is an important factor in appropriate disease management.[9] Frequency of reassessment and follow-up visits should be based on disease status.[2] Patients with stable disease may be seen less frequently with evaluations every three to six months and echocardiograms annually as compared with evaluations every one to three months and echocardiograms every six to 12 months in unstable disease. Reassessment of functional class and 6MWT should be performed at every visit in all patients with BNP evaluations based on facility protocol. Right heart catheterization should be performed in all patients upon clinical worsening and additionally in unstable disease every six to 12 months.[2]

In addition, several clinical tools are available and may help guide treatment decisions.[9,10] A validated risk score calculator has been created based on data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), which is one of the largest and most comprehensive PAH registries.[10] The calculator scores risk from 0 (lowest) to 22 (highest) based on WHO Group 1 subcategory, demographics, comorbidities, NYHA/WHO functional class, vital signs, 6MWT, BNP, echocardiogram, pulmonary function test, and right heart catheterization.[10] Scores are predictive of one-year survival in these patients.[10] Incorporation of the calculator into daily clinical use could aid in harmonizing objective and subjective assessments.[10] Additional risk assessment tools have been developed based on the Pulmonary Hypertension Connection registry, the FRENCH PAH registry, and the National Institutes of Health (NIH) registry.[9]

Goals of Treatment

A number of treatment goals, both of clinical and patient-related significance, exist for PAH.[7] Symptom control is one of the top priorities, often focusing on dyspnea as well as improved exercise endurance and functional capacity.[2,4] Measures of improvement are objective and may include the 6MWT.[2] Treatment should also aim to slow disease progression and worsening, including improving patient symptoms, quality of life, and survival.[2-4] Improvement in functional class and 6MWT have been noted to correlate with an improvement in patient QOL/HRQOL.[7,8] Normalization of hemodynamics is another key goal of treatment.[2] Treatment with PAH-targeted therapies has been shown to achieve these clinical goals as well as to improve QOL.[8] Finally, while data focusing on survival outcomes is limited, improving survival and preventing mortality remain important goals of treatment.[2,4,8]

The Three Pathways of Treatment

PAH-targeted treatment works via the three main disease pathways, namely prostacyclin, endothelin, and NO dysfunction.[3] Prostacyclin analogues have been considered a gold standard of treatment and there are currently three compounds available in the United States: epoprostenol (Flolan® and Veletri®, for injection), treprostinil (Tyvaso® inhaled solution and Remodulin® injection) and iloprost (Ventavis® inhaled solution).[8,11-15] Iloprost, which carries the highest cost compared to other treatments, was observed to have a slight improvement in outcomes by quality adjusted life years (QALYs) per 100 patients as compared with the other two agents.[8,16] Guidelines recommend reserving continuous intravenous epoprostenol and intravenous treprostinil, which are PAH-targeted treatments shown to improve survival, for the most critically ill (WHO functional class III or IV) patients.[2,8,17] Recent studies suggest, however, that delayed referral and administration of IV prostacyclins are associated with worse outcomes, suggestive that initiation of the most effective therapy should not be delayed until patients are critically ill.[37] When selecting a prostanoid, route of administration and adverse event profile should also be considered.[2] Epoprostenol requires the placement of an indwelling catheter while treprostinil and iloprost require clinic visits at the start of treatment.[16] In addition, the risk of and potential costs associated with injection reactions or infusion line infections should not be overlooked.[16]

Three ERAs, bosentan (Tracleer® tablets for oral use), ambrisentan (Letairis® tablets for oral use), and the most recently approved macitentan (Opsumit® tablets for oral use) are available in the United States.[18,19,31] Bosentan appears to be both cost-effective and produce a greater improvement in QALYs as compared to the prostanoids treprostinil and epoprostenol.[8] As compared with sildenafil, ERAs appear to produce a similar gain in QALYs, but are more costly.[16] An incremental cost-effectiveness was also observed with bosentan when compared with CCBs and oxygen.[8] In October 2013, Opsumit was approved for the treatment of PAH to delay disease

progression. It is a novel dual ERA that has a slower dissociation rate and sustained receptor binding compared to bosentan and ambristentan. This mechanism allows macitentan to remain effective at blocking endothelin receptors even when endothelin receptor 1 concentrations are high, which is a characteristic of PAH conditions. Macitentan is known for its first outcomes-based phase III study in PAH, which is different compared to other trials that focused on 6-minute walk distance as a surrogate primary end point. It is the first therapy indicated to delay disease progression and reduce hospitalizations for PAH. Several treatment considerations occur with ERAs, including abnormal liver function (particularly with bosentan), teratogenicity, and hemoglobin/hematocrit disturbances.[16] Liver function tests (LFTs), pregnancy testing, and complete blood counts (CBCs) must be routinely monitored on a monthly basis when ERAs are used, and the cost of the lab work should be factored into the cost of treatment.[2,16]

The NO pathway is targeted by PDE5-Is, of which two products—sildenafil (Revatio® tablets for oral use, oral suspension and injection) and tadalafil (Adcirca® tablets for oral administration)—are currently marketed in the United States.[20,21] PDE5-Is are effective and are less costly than the ERAs, and sildenafil appears to be the most cost-effective option when compared with the other two classes of PAH-targeted therapies.[6,8,16,17] In October 2013, riociguat (Adempas® tablets for oral administration) was approved for treatment of PAH to improve exercise capacity, WHO functional class, and to delay clinical worsening. It is also the first available FDA-approved medication to treat chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class. Riociguat has a dual mechanism of action in the nitric oxide-sGC-cGMP pathway that makes it different from PDE5-Is since they are dependent upon

Table 2 Indications, Administration, and Costs of Oral Therapies for PAH[18-21,31,32,35]

Product Name	Dosing	How Supplied	Treatment of PAH (WHO Group 1) to improve exercise abiity and to decrease clinical worsening	Treatment of PAH (WHO Group 1) to improve exercise ability	Persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class	Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH. Also reduced hospitalization for PAH	WAC/ Month	WAC/ Year
Opsumit (macitentan)	10mg QD	10mg tablet				✓	$6,840	$83,220
Adcirca (tadalafil)	40mg QD	20mg tablet		✓			$1,899	$23,105
Adempas (riociguat)	1mg to 2.5mg TID	0.5mg, 1mg, 1.5mg, 2mg, and 2.5mg tablets	✓		✓		$7,500	$91,250
Letairis (ambrisentan)	5mg to 10mg QD	5mg and 10mg tablets	✓				$6,893	$83,868
Revatio (sildenafil)	20mg TID	20mg tablet	✓				$2,103	$25,585
Tracleer (bosentan)	62.5mg to 125mg BID	62.5mg and 125mg tablets	✓				$7,050	$85,775

Key: **BID**=twice a day; **CTEPH**=chronic thromboembolic pulmonary hypertension; **QD**=once a day; **PAH**=pulmonary arterial hypertension; **TID**=three times a day; **WAC**=wholesale acquisition cost; **WHO**=World Health Organization

adequate supplies of endogenous nitric oxide. One problem with riociguat is that it has joined a very crowded oral marketplace for PAH (Table 2, page 16); however, it does have a place for patients with CTEPH.[32]

The use of combination therapy may be warranted in patients, although there are currently no specific recommendations.[2,8,22] The latest guidelines continue to recommend the initiation of monotherapy, continued evaluation of response to that therapy, and additional therapeutics introduced if patients do not have a substantial response. However, the current guidelines do not have specific recommendations for combination upfront therapies. The guidelines do recognize that patients at higher risk, including NYHA Class IV patients who are rapidly deteriorating, can benefit from the combination of these therapies very quickly.[2] In some patients with pulmonary arterial hypertension, the addition of sildenafil to long-term intravenous epoprostenol therapy improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, but not Borg dyspnea score.[33] By using combination therapy, the patient would receive treatment targeting multiple pathways, which may increase clinical benefits while minimizing adverse event risk.[6,16,22] In fact, data from the AMBITION study evaluating the use of initial combination therapy will be released shortly.[34] Healthcare utilization analyses have suggested that combination therapy, along with dose modifications, may be required for adequate disease management.[6]

Challenges and Potential Solutions

Early and accurate diagnosis and management of PAH is an important factor in treating these patients, particularly as diagnosis often occurs during more advanced stages when irreversible damage may have occurred.[1,4] In addition, due to the complexity of disease and treatment, it is recommended that patients be seen in specialty centers (a PH Care Center) and by a well-educated and experienced multidisciplinary team including specialists, nurses, and social workers.[2,9] Payors can assist in educating physicians and ensuring adherence to guidelines.[1] Emphasizing proper diagnosis, based on guideline criteria and definitive testing by experienced practitioners, will help ensure the correct initiation, selection, and administration of treatment.[2] Improvement in this area will not only help provide for better patient care and outcomes, but can also help contain costs.[7-9] As the oral medications may be dispensed on an outpatient basis, payors can educate pharmacists and pharmacies on PAH and the importance of compliance in these patients.[23] Pharmacists can then provide feedback to payors and practitioners, further enhancing the quality of patient care.[23]

Payors can set usage restrictions in place to help contain costs and ensure appropriate utilization of the PAH-targeted therapies, which can be costly.[8] First-line therapy with PDE5-Is or ERAs, which follows the guidelines for low-risk patients, could be a cost-effective way to help manage prescription access.[8,16,17] Prostanoids could be reserved for second- or third-line therapy in lower-risk or confirmed high-risk patients, based on guidelines, cost, and complexity of use.[8] When selecting a prostanoid, treatment choice may be made based on practitioner and patient preference or cost; the cost and efficacy profile of epoprostenol over iloprost makes it preferable; however, it also bears a higher risk of complications.[8,16] Prior authorizations (PAs) are already in place with many insurers.[24,25] PAs help ensure these medications are prescribed correctly based on indications and guidelines.[25] Patients may need to exceed an out-of-pocket payment limit prior to insurer reimbursement. In addition, in cases of combination treatment, which may be a cost-effective treatment method, the second or subsequent PAH-targeted therapy may have different usage restrictions than the first therapy, such as varying PA restrictions or not being covered. Payors should bear in mind that the various PAH-targeted treatments are not necessarily directly interchangeable, and treatment guidelines and best clinical practices should be consulted when creating formularies.[25]

Challenges can always arise regarding patient compliance issues. Selection of treatments with once-daily dosing or any of the orally dosed medications may help improve compliance and patient outcomes.[8,16]

Recently Approved and Future Treatment Options

Several new treatment options, working via current and novel pathways, have been recently approved or are currently being investigated. Macitentan is a potent ERA that appears to be effective and well-tolerated in clinical studies.[17,22] A survival benefit (i.e., decreased morbidity and mortality) has also been observed with macitentan which, along with once-daily dosing, makes it a promising new treatment option.[17,22] The PDE5-I vardenafil is also being investigated for its use in PAH.[22] Improvements in hemodynamics and 6MWT have been observed with treatment, although further studies are needed.[22] Also targeting the NO pathway is riociguat, a first-in-class agent that modulates NO signaling.[22] Clinical studies have shown riociguat to be well-tolerated and to improve subjective and objective outcomes, as well as QOL

measures.[17,22] Fasudil, a non-specific Rho/Rho-kinase pathway inhibitor, also targets the NO pathway and has shown promise in early-stage clinical studies.[17] NO pathway and cAMP targeting by the circulating peptide adrenomedullin is being investigated as inhaled and intravenous formulations.[17] Selexipag is an orally administered, highly selective prostacyclin receptor agonist that differs from the currently marketed prostacyclins; efficacy of selexipag is not modified under disease-state conditions, which may occur with the currently available prostanoids.[17,22] Improvements in pulmonary hemodynamics have been observed, and the adverse event profile appears similar to that of the other agents in its class.[17,22] A study examining survival outcomes of selexipag is currently ongoing.[22] Inhaled vasoactive intestinal peptides, such as aviptadil, are also under investigation; however, efficacy results are mixed.[17] Finally, tyrosine kinase inhibitors (TKIs) and serotonin antagonists have been investigated for their use in PAH.[17,22] TKIs target the platelet-derived growth factor pathway that has been implicated in PAH.[22] In particular, imatinib has been investigated; however, while efficacy has been noted, due to the risk-benefit ratio, use in PAH is questionable.[17,22] Similarly, use of the serotonin antagonist terguride did not produce expected results; however, investigation of the serotonin pathway in PAH treatment may continue to develop.[17]

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Biosimilars: Exploring Regulation, Pricing, and Marketing

By Chronis H. Manolis, RPh, Vice President of Pharmacy, University of Pittsburgh Medical Center Health Plan; and Debra Gordon, MS

Large-molecule compounds, or biologics, are one of the most dynamic areas in the pharmaceutical industry. The world market for biopharmaceuticals, which are designed to target specific proteins in complex diseases such as cancer and autoimmune conditions, is estimated at more than $140 billion, with spending expected to reach $200 to $210 billion by 2016.[1]

Ten of the top 15 drugs used in the United States (based on price) in 2011 were biopharmaceuticals, and in 2012, sales increased by 18.4 percent, even as spending on small-molecule compounds fell about 1 percent.[2,3]

But specialty drugs are the most expensive medications on the market, typically relegated to the top formulary tiers. That's why health plans are eagerly awaiting the introduction of biosimilars, "follow-on" versions of specialty drugs that have gone off patent.

Biosimilars differ from generic drugs in that they are not identical copies of the reference compound. Instead, they are defined as "highly similar" with no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.[4] They can't be identical, however, because of the complex manufacturing process required, with most grown in living organisms such as plant or animal cells. Small-molecule drugs, by contrast, are typically manufactured through chemical synthesis.

Although available in Europe since 2006, Japan since 2009, and South Korea since 2010, no biosimilars have yet reached the U.S. market. The lag is blamed on the U.S. Food and Drug Administration (FDA), which did not release draft regulations for the approval process until February 2013.[5]

Those regulations came courtesy of the Patient Protection and Affordable Care Act (ACA), which included the Biologics Price Competition and Innovation Act (BPCI Act). The BPCI creates an abbreviated approval pathway for biosimilar products, allowing biosimilar products to be approved without the extensive nonclinical and clinical studies required of its reference drug, although some studies will still be needed.[6]

The BPCI also grants a 12-year exclusivity period for the reference product, with an additional six months of exclusivity if it is licensed for a pediatric population. A biosimilar application cannot even be submitted until four years into the reference product's licensure. In addition, the first licensed biosimilar receives a one-year exclusivity period before additional products can be approved.

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The Pathway To Approval

The FDA released four draft guidance documents in 2013 detailing biosimilar regulations: quality guidelines, scientific guidelines, questions and answers related to the implementation of the BPCI Act, and rules on biosimilar sponsor interactions with FDA regulators.[7]

The regulations establish two levels of biosimilars: one in which the product is "highly similar" to the reference drug, and the other in which the two are considered interchangeable to the point that automatic substitution would be allowed.

The path to approval requires:

1. Analytical studies to demonstrate the similarity of the product
2. Animal studies to assess toxicity, PK/PD, and immunogenicity
3. Clinical studies to demonstrate safety, purity, and potency

The agency does, however, have the authority to waive any requirement.

The draft guidance also recommends that drug manufacturers consider the following in assessing the similarity of their drug to the reference drug:

- Expression system
- Manufacturing process

- Physicochemical properties
- Functional activities
- Receptor binding and immunochemical properties
- Impurities
- Characterization of the reference product and reference standards
- Characterization of the finished drug product
- Stability

As of late 2013, the FDA had yet to finalize the regulations and no applications had been submitted for review.[8]

The Biosimilar Market

The biosimilar market will be driven by two things: expiring patents on many biologics, with drugs worth an estimated $81 billion in global annual sales coming off patent by 2020, and the increased push for lower costs as the United States moves toward a value-based reimbursement system to reduce healthcare expenditures.[9]

Although companies that make generics tend to focus only on generics, large pharmaceutical companies that manufacture branded specialty drugs are expected to dominate the biosimilars market. They include Sandoz (Novartis), Hospira, Teva, Amgen, Pfizer, and Boehringer Ingelheim.[10] Many have already formed partnerships with smaller companies that have experience with biosimilars in other countries.

For instance, Hospira and India-based Celltrion are developing a biosimilar erythropoietin (EPO), and Amgen and Actavis have partnered to market Synthon's trastuzumab biosimilar. The Indian company Biocon, which is also developing an EPO, as well as filgrastim and insulin biosimilars, initially partnered with Pfizer; now it has joined with Bristol Myers Squibb to market an insulin.[10]

However, developing these drugs carries its own challenges, as many companies find. In 2012, Merck disbanded its dedicated biosimilar unit, and Samsung Electronics and Teva quit working on their Rituxan biosimilars. Reasons included confusion over regulatory pathways and the complexity of developing the drugs.[11]

Companies with reference drugs are expected to compete against biosimilars on many fronts, including their entrenched position in the market, clinician and patient preference, and price. For instance, Roche plans to market Herceptin® (trastuzumab) and Rituxan® (rituximab) at lower prices to compete for patient access and market share.[10] They are also finding ways to extend patents in order to discourage biosimilar development.[11]

Figure 1: Biosimilar Molecules Approved, Filed, or In Clinical Development*

*Biosimilar molecules approved in highly regulated markets E.U., U.S., Japan, Australia; in registration, in clinical development phase I, II, or III as reported in public clinical trial databases www.clinicaltrials.gov, www.clinicaltrialsregister.eu, company and press reports; excludes insulin, generic glatiramer, non-biosimilar long-acting filgrastims, and pegylated human growth hormone which are not eligible for biosimilar regulatory pathways.

Figure 1 depicts the current biosimilars pipeline. There are nearly 1,000 biosimilars and biobetters (defined as a follow-on biologic that improves upon a reference drug) under development in the E.U., United States, and other countries—about 430 in the United States. Most, however, are in preclinical development. The majority is in the insulin/analog, epoetin alpha, interferons, molecular antibody and antibody fragments, and cancer-targeted non-MAb categories.[8]

Payors and Biosimilars

Coverage of biosimilars will depend on numerous factors. One survey of U.S. payors found that the more payors believe that the biosimilar and reference drug are highly similar, the more likely they are to offer coverage.[12] Payors also trust products from large pharmaceutical companies that have experience in the biologic arena more so than those coming from non-pharmaceutical companies or companies in emerging markets.[12,13]

Cost will, of course, drive coverage decisions, with payors insisting on at least a 20 percent differential for formulary inclusion.[13]

In Europe, total sales of the 14 biosimilars on the market in 2009-2010 were $200 million, with an average price discount of 25 percent. Remsima, one of the first approved biosimilar antibodies, launched in 2013 with a 30 percent price differential from its reference drug, Remicade® (infliximab).[14] By 2020, the E.U. expects savings up to $43 million in drug costs from biosimilars.[15]

In the United States, mail order pharmacy Express Scripts estimated that just 11 biosimilars, including those

for Remicade, Humira® (adalimumab), and Rituxan® (rituximab) could save $250 billion by 2024, assuming the first biosimilars hit the market in 2019. Just when the first biosimilar will be approved is up for debate, with estimates ranging from 2015 to 2019.[14]

Another deciding factor for coverage is interchangeability, because that would position biosimilars as closer to generic drugs and allow automatic substitution at the pharmacy.

Yet even the FDA has not said how a product can become interchangeable. "It would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment," the agency wrote in a 2012 FAQ on the BPCI. "The FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."[16]

Challenges Remain

Even with the FDA draft guidance documents, several challenges remain in the regulation and marketing of biosimilars. These include:[5]

Nomenclature. Can the generic name of the molecule be used for the biosimilar as it is for generic small-molecule drugs?

Labeling. Should manufacturers be required to clearly identify their products as biosimilars and highlight the differences between them and biologics?

Indications. Will all indications of the reference product be extrapolated to the biosimilar in the absence of clear clinical evidence for each indication? The world's first biosimilar to infliximab was approved for marketing in South Korea for all six indications of infliximab, although the product was only tested in rheumatoid arthritis with limited pharmacokinetic comparisons for the other indications.[21] The extrapolation of safety and efficacy data across indications is challenging, and may be inappropriate for biosimilars without strong scientific justification, because the mechanism of action, immunogenicity, and safety profiles among the products may vary based on the different indications. The decision whether or not to extrapolate indications will have a major impact on the management of biosimilars within managed care and the ability to optimize the savings potential associated with these new products.

Biosimilars: Implications for Various Stakeholders

There are numerous implications of biosimilars for payors, pharmaceutical companies, providers, specialty pharmacies, and patients, as well as many unanswered questions. Specifically:

Payors. Payors need to articulate the value proposition of biosimilars and leverage those benefits to all stakeholders. Unlike traditional generics, lower cost alone won't be enough. They also need to consider how to navigate barriers for entry, including multiple manufacturers and indications for biosimilars, particularly if the indication differs from the innovator product. Unanswered questions include the proper placement of biosimilars on formularies and rebate implications. Although payors have a great opportunity for cost savings generated by increased competition, they also face significant risk if they are unable to optimize the value potential of lower cost options.

Pharmaceutical companies. Pharmaceutical companies also have a significant opportunity to enter new markets. However, the complexity of manufacturing may limit entrants to those with extensive experience manufacturing biologics. Biosimilar manufacturers also need deep market/managed care experience, clinical trial design experience and the ability to conduct such trials, a deep understanding of intellectual property and patent implications, and must be prepared to make a significant investment in patient and provider education.

A key question for manufacturers of the innovator products is whether they will lower their prices to retain market share and/or manufacturer their own biosimilar. Another question is whether enhanced, next generation drug technology will mute the opportunity of the new biosimilar market.

Physicians. Physicians need assurance that biosimilars are safe and effective. They will want to see the evidence from clinical trials. They may also be hesitant to switch patients who are stable on the branded biologic given the potential risk and the possible need for increased monitoring. Payors and manufacturers also need to explore how biosimilars fit into the value-based purchasing where physicians and accountable care organizations are taking more risk. Will these aligned incentive models increase biosimilar adoption?

Specialty pharmacy. Can specialty pharmacies take advantage of the increased competition or will payor formularies drive product selection? If formularies contain all options—branded and biosimilar—that may increase inventory cost and reporting requirements for specialty pharmacies. Also in question is how contracting with biosimilar manufacturers will affect current relationships between specialty pharmacies and branded manufacturers. Finally, specialty pharmacies need to identify ways to leverage their experience and become a coveted, valuable partner to the biosimilar manufacturers.

Patients. It is crucial that patients have confidence in the product safety and effectiveness given the severity of their disease and emotional attachment to the innovator product. This is a level of education that is rarely required in the generic market, but cannot be underestimated in the biosimilar market. Another issue is the availability of patient support programs—particularly financial assistance—for the biosimilar agents. In addition, given the cost profile for biosimilar agents, copays may not be less. Consequently, will there be incentive for members to ask for the less costly biosimilar? Lastly, given the overall lower cost profile of biosimilars, will the proliferation of High Deductible plans and ACA-integrated Out-of-Pocket maximum plan designs enhance biosimilar adoption?

Substitution. Will pharmacists be allowed to substitute a biosimilar for a biologic without physician approval? The ACA allows interchangeable biosimilars to be substituted for the reference product without healthcare provider intervention, but it is up to states to decide if they will allow such substitutions. While more than 20 states have considered or are considering such legislation, just five have passed such laws, three of which include a sunset date likely to occur before the first interchangeable biosimilar reaches the market.[17]

Pharmacovigilance. Will long-term monitoring and batch-by-batch surveillance be required? In October, the Academy of Managed Care Pharmacy established a Biosimilars Task Force to develop a Biosimilars Collective Intelligence System to document their safety and efficacy, using continuous analysis of available data for innovator specialty drugs as reference points.

Physician and patient uptake. Companies selling biosimilars in the United States will have to educate providers about biosimilars and overcome their reluctance to use the new products. In a survey of 405 U.S. physicians, 54 percent rated their understanding of the differences between biosimilars and generics as "fair" to "poor," while 67 percent rated their knowledge of the differences between biosimilars and reference biologics similarly.

Even fewer (76.3 percent) understood the regulatory approval pathway. Thus, it is not surprising that 97 percent felt that continuing education on biosimilars was at least "somewhat important," with 75 percent saying it was important or very important.[18] Other surveys find that clinicians want to see large clinical trials on the biosimilars before they will feel comfortable prescribing them.[19]

Patients, who often pay substantial amounts out of pocket for biologic drugs, appear to have less reluctance to switching. Nearly 70 percent of 1,637 insulin-using patients with diabetes surveyed said they would definitely or likely switch to a less expensive, "generic" version of the drug if their healthcare provider recommended it.[20]

However, given that the drugs will likely be placed high on tiered formularies, biosimilar manufacturers may need to provide discounts and coupons just as branded manufacturers do, something that is not done in the generic market.[13]

Conclusion

The development of a regulatory pathway for biosimilar development in the United States could lead to a flood of lower cost biologic drugs with the potential for millions in health plan savings. However, the cost of developing, manufacturing, and marketing these products will result in a lower price differential than payors are used to seeing between branded drugs and generics.

In addition, payors will have to provide significant education around the safety and efficacy of biosimilars in order to convince physicians to prescribe them and patients to use them.

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The Evolving Landscape of Metastatic Castrate-Resistant Prostate Cancer Management

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In 2013, an estimated 238,000 men were newly diagnosed with prostate cancer. Of these, an estimated 45,000 had metastatic disease, a significant number given that the potential costs of treatment can be more than $100,000 per year. The Surveillance, Epidemiology and End Results program (SEER) shows that more than 15 percent of men will be diagnosed with prostate cancer in their lifetime, typically at the median age of 66 years. However, unlike other cancers, prostate cancer is a slower growing cancer, having a 99.2 percent five-year survival.[1]

Due to increases in prostate cancer screening, 80 percent of prostate cancer is in stage 1, or localized disease.[1] Staging in prostate cancer, like many other cancers, is an important factor in determining the treatment that a physician and patient might choose. If the cancer progresses and becomes metastatic, yet remains hormone sensitive, androgen deprivation therapy (ADT) can typically be employed. ADT is the use of drugs or surgery to substantially decrease production of androgens and limit the growth of the androgen-dependent cancer.[2] ADT will not cure metastatic prostate cancer, but can shrink and control tumor growth.

Metastatic castration-resistant prostate cancer (mCRPC) is defined as 1) a continuous rise in the prostate-specific antigen (PSA) level; 2) progression of pre-existing disease; and/or 3) appearance of new metastases while on androgen deprivation therapy.[3] In the last several years, treatment of patients with mCRPC has rapidly evolved with several novel drugs, a therapeutic cancer vaccine, and a radiopharmaceutical approved by the FDA. These include Jevtana® (cabazitaxel), Provenge® (sipuleucel-T), Zytiga® (abiraterone), Xtandi® (enzalutamide), and Xofigo® (radium Ra 223 dichloride).

Six agents have shown improvement in overall survival in the mCRPC setting. These include docetaxel (Taxotere®) and the aforementioned therapies. Until recently, mCRPC was typically treated with an every-three-week course of docetaxel based on an improved overall survival when compared to mitoxantrone (18.9 vs. 16.5 months: 2.4 month improvement, p=.009).[4] Treatment is associated with the typical side effects of chemotherapy: nausea, hair loss, and bone marrow suppression.

In April 2010, Provenge was approved by the U.S. Food and Drug Administration (FDA) to become the first in a new class of cancer immunotherapeutic agents. Provenge is an autologous cancer vaccine. To produce the vaccine, the white blood cell fraction containing antigen-presenting cells is collected from

Table 1 Treatment Summary

Generic Name (Trade Name)	Disease State Indication	Mechanism of Action	Overall Survival Improvement (Control)	Treatment Regimen	Duration of Therapy	Cost Per Cycle/Month
Docetaxel (Taxotere)	mCRPC	Microtubule stabilization	2.4 months (mitoxantrone)	75mg/m^2 IV infusion every 3 weeks with prednisone 5 mg twice daily	Avg. 10 cycles	$2,900/cycle
Sipuleucel-T (Provenge)	Asymptomatic/minimally symptomatic mCRPC	Activated patient dendritic cells	4.1 months (placebo)	IV infusion every 2 weeks x 3 doses	3 treatments	$34,423/ treatment
Cabazitaxel (Jevtana)	Docetaxel-resistant mCRPC	Microtubule stabilization	2.4 months (mitoxantrone)	25 mg/m^2 IV infusion every 3 weeks with prednisone 10 mg daily	Avg. 6 cycles	$8,660/cycle
Abiraterone (Zytiga)	mCRPC	Androgen biosynthesis CYP17A inhibitor	Post-docetaxel: 4.6 month improvement (placebo) Pre-docetaxel: Median/statistical significance not reached; 25% risk reduction (placebo)	1,000mg orally daily with prednisone 5mg twice daily	Avg. 8 months	$6,836/month
Enzalutamide (Xtandi)	Chemotherapy resistant-mCRPC	Androgen receptor blocker	Post-docetaxel: 4.8 month improvement (placebo) Pre-docetaxel: 2.2 month improvement; 30% risk reduction (placebo)	160mg orally daily	Avg. 8 months	$7,889/month
Radium RA 223 dichloride (Xofigo)	mCRPC with symptomatic bone metastases and no visceral metastases	Alpha particle-emitting radioactive agent	3.6 months (placebo)	1.35 microcurie/kg every 4 weeks	6 cycles	$11,500/cycle

the patient, cells are exposed to the prostatic acid phosphatase (granulocyte macrophage colony-stimulating factor [PAP-GM-CSF recombinant fusion protein]) and then reinfused into the patient.[4] The result, as measured by Dendreon's phase III trial, showed an improvement in median overall survival (25.8 vs. 21.7: 4.1 months improvement; HR=0.78) and a 22 percent reduction in mortality risk.[5] This novel agent, given three times every two weeks, has a wholesale acquisition cost (WAC) of $34,423, or $103,269 for the full course. Provenge currently carries a category 1 NCCN recommendation for asymptomatic or minimally symptomatic patients with mCRPC.

Following Provenge, the FDA approved Jevtana, a semi-synthetic taxane derivative, in June 2010 for men with mCRPC previously treated with a docetaxel-containing regimen. Sanofi's trial, which compared Jevtana dosed once every three weeks with mitoxantrone, showed a 2.4 month increase in overall survival (15.1 vs. 12.7: 2.4 month improvement; HR=0.72).[6] However, this survival improvement was associated with an increase in sepsis, renal failure, and febrile neutropenia. The NCCN guidelines have Jevtana listed as a category 1 treatment option post-docetaxel therapy. A cycle of therapy has a WAC of $8,660 based on an average body surface area.

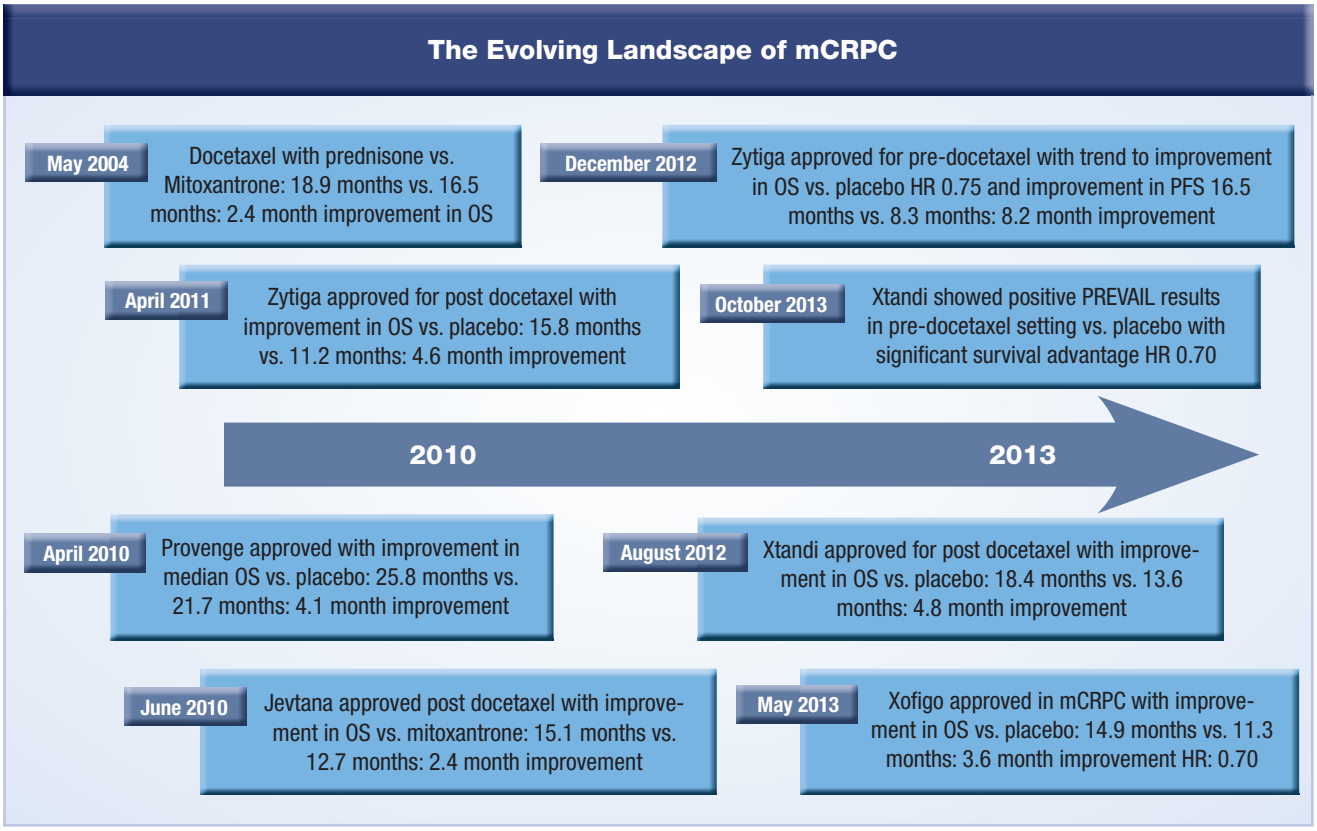
The first oral mCRPC therapy for patients previously treated with docetaxel, Zytiga, was approved in April 2011. Similar to Jevtana and docetaxel, Zytiga is administered with a low-dose prednisone. In a large 797-person trial, Zytiga demonstrated an improvement in overall survival compared with placebo (15.8 months vs. 11.2 months: 4.6 month improvement; HR=0.74) and radiologic progression-free survival (5.6 months vs. 3.6 months: 2.0 month improvement; HR=0.66) with the most common adverse events of fatigue, anemia, and back pain in less than 9 percent of patients.[7] Post-docetaxel treatment with Zytiga carries a category 1 NCCN recommendation.

Five-year survival of prostate cancer patients

Percentage surviving five years

99.2%

A little more than a year later, Zytiga gained FDA approval in the pre-docetaxel setting based on a trend toward improvement in overall survival (median not reached vs. 27.2 months; HR=0.75) and a statistically significant increase in radiographic progression-free survival (16.5 months vs. 8.3 months: 8.2 month improvement; HR=0.53) compared to prednisone

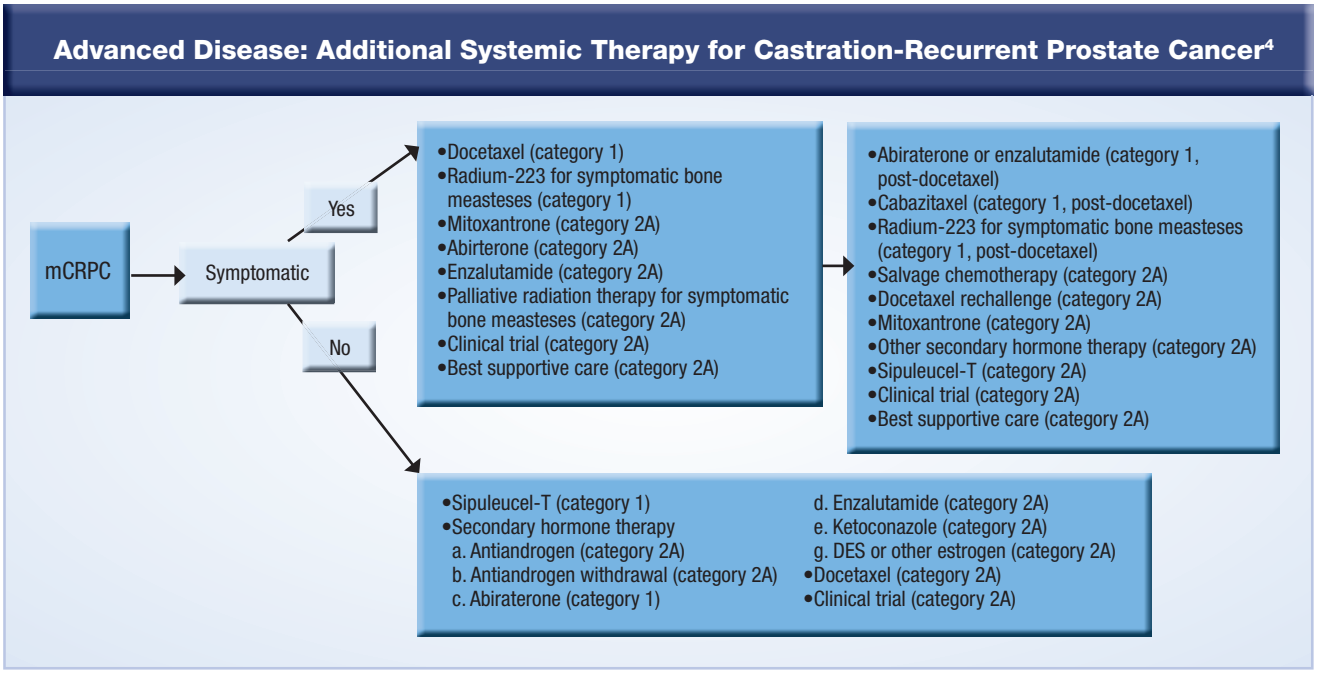


prednisone alone after a planned interim analysis unblinded the study when 43 percent of expected deaths had occurred.[8] The NCCN includes Zytiga as level 1 evidence for use in the pre-docetaxel setting for men with asymptomatic or minimally symptomatic mCRPC. The monthly WAC of Zytiga is $6,836.

Following Zytiga's pre- and post-docetaxel approvals, Xtandi was approved in August 2012. The 1,199-patient AFFIRM trial showed a significant improvement in median overall survival (18.4 vs. 13.6 months: 4.8 month improvement; HR=0.63) and radiographic progression-free survival (8.3 vs. 2.9 months: 5.4 month improvement; HR=0.40) among other endpoints.[4] Adverse events were mild and most commonly included fatigue, diarrhea, hot flashes, and headache. The positive results from this trial and the approval of Zytiga use pre-docetaxel left the clear question of the benefit of Xtandi in the pre-docetaxel setting.

The answer came in October 2013 with the planned interim analysis of the 1,700-patient phase III PREVAIL study. Xtandi showed a statistically significant improvement in calculated median overall survival compared with placebo (32.4 months vs. 30.2 months: 2.2 month improvement; HR=0.70),[9] and a 30 percent reduction in the risk of death. The median progression-free survival has yet to be reached for Xtandi, yet an 81 percent reduction in the risk of radiographic progression or death was observed compared to placebo. Currently, the NCCN guidelines state that while Xtandi awaits approval for use in this pre-chemotherapy setting, it is a suitable option for men who are not good candidates to receive docetaxel.[9] The presentation of the results of the PREVAIL trial in January 2014 will most likely augment these recommendations and provide sufficient evidence for use of Xtandi in the pre-docetaxel setting. The monthly WAC of Xtandi is $7,889.

The most recent treatment approved for mCRPC was Xofigo, an alpha particle-emitting radioactive agent, approved in May 2013 for use in mCRPC patients with symptomatic bone metastases and no visceral disease. Of note, the NCCN guidelines highlight Xofigo as a category 1 first-line option for use in this patient type. In a 921-patient trial, Xofigo, when added to the "standard of care," showed an improvement in overall survival (14.9 months vs. 11.3 months: 3.6 month improvement, HR=0.70).[4] Adverse events included anemia, thrombocytopenia, and neutropenia in less than 13 percent of patients. This safety profile is better than standard radiation therapy and may be especially helpful at the end of life when disease is particularly painful. Notably, no head-to-head trials have been conducted.



Xofigo will be primarily used in addition to other mCRPC therapies rather than as a replacement of such therapies in the treatment of bone metastases. Therefore this product will have a limited impact on the sequencing of products used to treat mCRPC, but may have a substantial impact on the financial burden incurred by health plans. Xofigo is given at four-week intervals for six injections and has a WAC of $11,500 per month, or $69,000 for the six-month treatment course.

With the evolving landscape, oncologists and managed care organizations (MCOs) alike have adapted the way they assess prostate cancer management. While oncolytic agents as a therapeutic category have historically enjoyed limited payor controls, MCOs are rapidly developing utilization management controls for newer agents. With Zytiga's pre-docetaxel indication, several MCOs have implemented step edits requiring the use of Zytiga prior to Xtandi; this decision may be primarily driven by economics rather than clinical outcomes. With the recently released PREVAIL results, oncologists and urologists may prefer Xtandi because it can be used without prednisone.

The recent PREVAIL results may generate increased interest in the use of pathways and preferred agents among payors. The NCCN guidelines give both Zytiga and Xtandi the same level of recommendation (2A) in symptomatic pre-chemotherapy mCRPC. The guidelines further state that evidence-based guidance on the sequencing of these agents remains unavailable.[4] Without true comparative trials, payors are left to make decisions based on cross-trial comparisons, which may inherently incorporate bias, particularly related to baseline differences in patient populations. In the absence of such data, payors are left to weigh costs, indirect comparison of efficacy, and safety when choosing preferred agents. While Zytiga is the less costly option compared to Xtandi, MCOs will need to re-evaluate the mCRPC category with the additional PREVAIL data and identify the best option for their patients.

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Economic Impact of Off-Label Utilization and Site of Care of Immune Globulin Therapy Within a Regional Health Plan

The U.S. Food and Drug Administration (FDA) has approved six uses for immune globulin (Ig) therapy; however, it is currently used to treat more than 100 disease states. The six approved uses consist of:

- Primary immunodeficiency disease (PIDD)
- Idiopathic thrombocytopenic purpura (ITP)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Kawasaki disease (KD)
- Chronic lymphocytic leukemia (CLL)

The use of intravenous immune globulin (IVIg) therapy in North America has grown, on average, 11 percent each year, and is steadily increasing as it continues to be used for more indications.[1] Off-label uses constitute about 50-80 percent of total Ig utilization.[2] The largest share of Ig therapy use is in patients with primary immunodeficiency disorders and neurological conditions.[2] Currently, there are several ongoing clinical trials that are evaluating new uses for Ig therapy, including Alzheimer's disease (AD), autism spectrum disorder (ASD), and *Clostridium difficile* infection (CDI).

Due to the lack of consensus guidelines and the use of Ig therapy in many disease states, the economic burden is significant for managed care. As the use of Ig therapy expands with more FDA-approved and off-label use, healthcare expenditures continue to rise exponentially. The pricing of Ig products varies significantly in the United States, with the average wholesale acquisition cost ranging from $50 to $80 per gram.[3] The average annual cost for Ig therapy can range from $40,000 to $90,000 per patient depending on dose, infusion time, length of treatment, and site of care.[4]

The objective of this analysis was to identify how off-label utilization of Ig and various sites of administration impact financial expenditures within a regional health plan. To do so, a medical claims database from a regional health plan was used containing approximately 700,000 lives. All health plan claims were accessed in a manner fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). All continuously enrolled (CE) health plan patients who were administered Ig therapy between January 1, 2013 and June 30, 2013 were identified. Each claim was determined to be for either an appropriate or potentially inappropriate

diagnosis based on FDA-approved indications and available compendia data. The economic impact of various sites of service (home care, physician outpatient, or hospital outpatient) was also analyzed.

A total of 187 unique patients were administered Ig therapy during the measurement period, representing 964 total claims and $5.5 million. The mean age was 49.4; females made up 59.9 percent of the group. Of the 187 patients, there were 60 different diagnoses (nine different therapeutic specialties) from 56 different facilities. One hundred and fifty-six (16.2 percent) of the claims were identified to be potentially inappropriate, accounting for $1.3 million (23 percent of the total costs). 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. One hundred and eighty-five (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. Allergy/immunology and neurology specialties made up 85 percent of the Ig expenditures, resulting in $4.7 million.

Table 1 — Medical Claims Breakdown by Site of Service

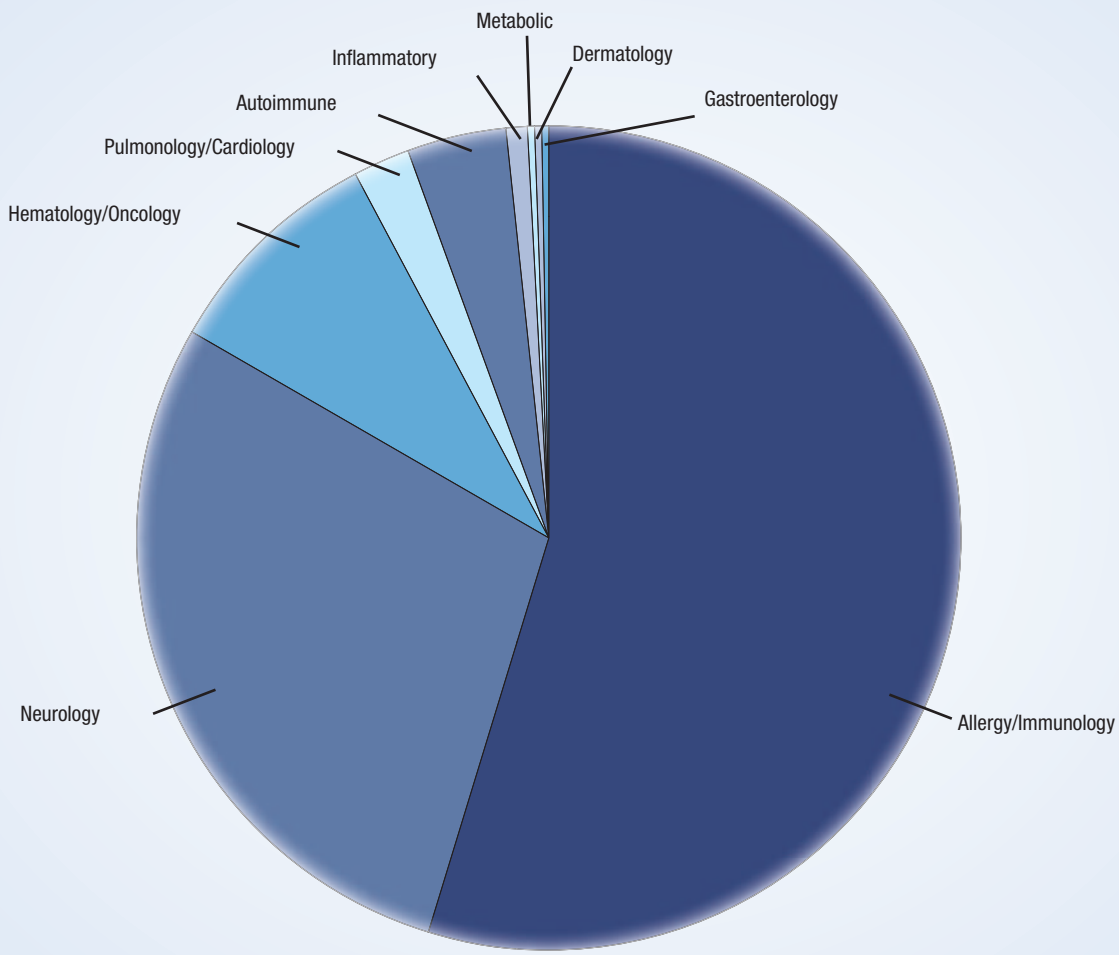
Place of Service	Number of Claims	Number of Unique Members	Average Number of Claims/ Member	Average Quantity/ Claim	Average Quantity/Member	Sum of Paid Amount	Average Paid Amount/Claim	Average Paid Amount/ Member
Office	185	40	4.63	97.29	449.98	$538,776.08	$2,912.30	$13,469.40
Patient's Home	359	59	6.09	216.22	1,315.63	$1,645,718.35	$4,584.17	$27,893.53
Hospital Outpatient or N/A	420	99	4.24	187.41	795.07	$3,331,535.30	$7,932.23	$33,651.87
Grand Total	**964**	**187**	**5.16**	**180.84**	**932.26**	**$5,516,029.73**	**$5,722.02**	**$29,497.49**

Table 2 — Medical Claims Breakdown by Diagnosis

Diagnosis Type	Number of Claims	Percent of Claims	Number of Unique Members	Percent of Unique Members	Average Number of Claims/ Member	Total Paid	Percent of Total Paid	Average Paid/Claim	Average Paid/Member
Allergy/Immunology	532	55.19%	106	56.68%	5.02	$2,889,788.73	52.39%	$5,431.93	$27,262.16
Neurology	279	28.94%	49	26.20%	5.69	$1,846,317.90	33.47%	$6,617.63	$37,679.96
Hematology/Oncology	84	8.71%	32	17.11%	2.63	$404,745.53	7.34%	$4,818.40	$12,648.30
Pulmonology/ Cardiology	21	2.18%	5	2.67%	4.2	$156,085.92	2.83%	$7,432.66	$31,217.18
Autoimmune	36	3.73%	5	2.67%	7.2	$118,919.66	2.16%	$3,303.32	$23,783.93
Inflammatory	6	0.62%	3	1.60%	2	$94,045.29	1.70%	$15,674.22	$31,348.43
Metabolic	4	0.41%	1	0.53%	4	$3,374.16	0.06%	$843.54	$3,374.16
Dermatology	1	0.10%	1	0.53%	1	$2,596.30	0.05%	$2,596.30	$2,596.30
Gastroenterology	1	0.10%	1	0.53%	1	$156.24	0.00%	$156.24	$156.24
Grand Total	**964**	**100.00%**	**187**	**100.00%**	**5.16**	**$5,516,029.73**	**100.00%**	**$5,722.02**	**$29,497.49**

This analysis demonstrates the use of Ig therapy for a wide variety of medical conditions, both on- and off-label. In addition to off-label utilization, site of care can be associated with higher costs. Administration in a hospital outpatient setting could result in an average cost per Ig claim that is 172 percent more than if administered in an outpatient physician office. Site-of-care optimization is one opportunity for managed care organizations to reduce unnecessary resource utilization and contain the escalating cost of Ig therapy.

Figure 1: Percent of Claims by Diagnosis Type



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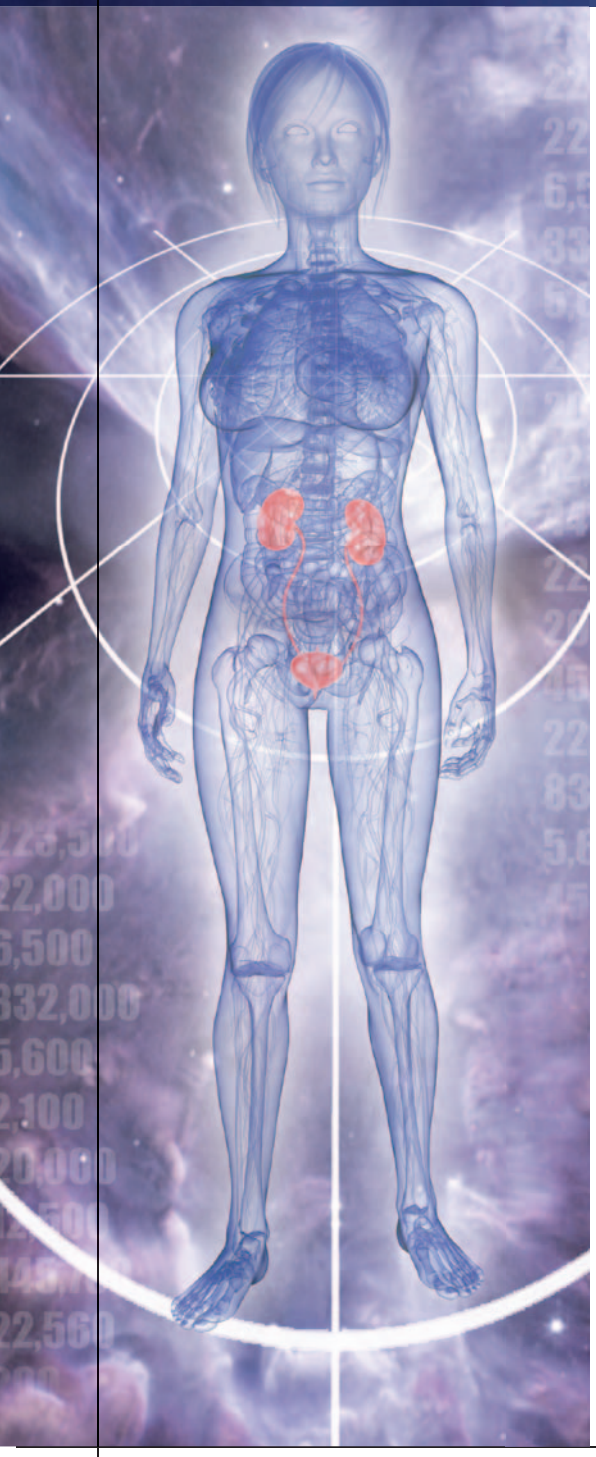
Managed Care Considerations for the Treatment of Renal Cell Carcinoma

Robert S. Alter, MD, Co-Chief of Urologic Oncology at the John Theurer Cancer Center



Robert Alter, MD

Renal cell carcinoma (RCC) is the sixth leading cancer diagnosis in men and the eighth leading cancer diagnosis in women in the United States. In 2013, an estimated 65,150 new patients will be diagnosed with RCC, each associated with healthcare-related costs up to $43,805 per year.[1,2] Similar to other cancers, early localized disease can be treated with surgical options resulting in a high chance of cancer-free survival. Unfortunately, RCC is difficult to detect at an early stage and is often found incidentally following abdominal imaging for an unrelated reason. A "classic triad" of flank pain, hematuria, and palpable abdominal mass was historically used to diagnose RCC, but only presents in around 10 percent of patients. Due to the asymptomatic nature of RCC, most patients progress to advanced RCC (aRCC) and, as a result, require systemic treatment.

Until recently, the standard of care for advanced or metastatic RCC had been administration of immunotherapies, such as interferon alpha (IFN-α) or high doses of interleukin (IL-2).[3] While these treatments provide modest clinical benefits, the significant toxicities can lead to a high discontinuation rate.[4] Other traditional chemotherapy or radiation regimens have not established evidence of improving progression-free survival and are not indicated for RCC.[3] As a result, the first-line treatment of aRCC has largely shifted to the newer targeted therapies. These therapies have been shown to improve patient outcomes and have more tolerable side effect profiles than traditional therapies, but increase the cost burden ($65,000 vs. $34,000, respectively).[4]

Targeted Therapies Available for aRCC

Approval of tyrosine kinase inhibitor (TKI) therapy for aRCC provided an opportunity for patients to have additional, more tolerable options compared with IFN-α or IL-2. Other benefits include the dosing schedule of these oral medications, once or twice daily, which may also offer adherence advantages compared to the injectable therapies.[3] TKIs inhibit a number of tyrosine kinases located on extracellular membranes, which are involved in protein synthesis, angiogenesis, and cell proliferation.[5] Overstimulation of these tyrosine kinase receptors has been shown to play a role in tumor growth and metastasis in patients with aRCC. The TKI therapies currently approved for aRCC include sorafenib (Nexavar®, Bayer/Onyx Pharmaceuticals), sunitinib

(Sutent®, Pfizer), pazopanib (Votrient®, Glaxo SmithKline), and axitinib (Inlyta®, Pfizer). The active comparator to many of these agents was immunotherapy or placebo. As additional targeted therapies come to market, the choice of agents becomes more complicated.[3]

Another type of treatment available for aRCC includes the inhibition of the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that has a unique set of pathways compared to tyrosine kinases.[6] However, these pathways help influence similar intracellular activities, such as cell proliferation, cell growth, cell cycle regulation, and protein synthesis. As with tyrosine kinases, overstimulation of mTOR receptors has been seen in patients with aRCC. Temsirolimus (Torisel®, Pfizer) and everolimus (Afinitor®, Novartis) are the two mTOR inhibitors currently approved for the treatment of aRCC in the United States. Temsirolimus is available only as a once-weekly IV formulation, given over a 30- to 60-minute infusion, while everolimus is available as a once-daily oral therapy.[3]

The third class of targeted therapy available for the treatment of aRCC is a humanized monoclonal antibody. The only drug in this class approved for use in aRCC is bevacizumab (Avastin®, Genentech).[7] Bevacizumab works by binding to and inhibiting vascular endothelial growth factor (VEGF), a key protein involved in angiogenesis of tumors. Bevacizumab and IFN-α together have been shown to be more effective than either therapy alone.[8] The required administration for this combination is more complicated, with bevacizumab infused over 30-90 minutes every two weeks and IFN-α injected subcutaneously three times weekly.

National Guidelines and Treatment Choices

The National Comprehensive Cancer Network (NCCN) guidelines contain a comprehensive list of treatment options for aRCC.[3] However, these guidelines are relatively vague and leave much of the decision making up to the treating physician. The ambiguous nature of the guidelines allows for the development of unique practice strategies, resulting in a lack of therapeutic consistency among providers. While a series of first-line treatments exists for patients with predominantly clear-cell carcinoma, there are fewer options for the treatment of non-clear cell carcinoma. Enrollment in a clinical trial is currently the preferred treatment choice for all non-clear cell RCC, although some TKI therapies show

Table 1 — Clinical Comparison of Targeted Therapies Used in the Treatment of Advanced RCC

Drug	Nexavar (sorafenib)	Sutent (sunitinib malate)	Torisel (temsirolimus)	Avastin (bevacizumab)	Afinitor (everolimus)	Votrient (pazopanib)	Inlyta (axitinib)
Manufacturer	Bayer/Onyx	Pfizer	Pfizer/Wyeth	Genentech	Novartis	GSK	Pfizer
U.S. Approval for RCC	2005	2006	2007	2009	2009	2009	2012
Indication*	Treatment of patients with aRCC	Treatment of patients with aRCC	Treatment of patients with aRCC	Treatment of patients with mRCC in combination with interferon-alpha (IFN-α)	Treatment of adults with aRCC after failure of treatment with sunitinib or sorafenib	Treatment of patients with aRCC	Treatment of aRCC after failure of 1 prior systemic therapy
Administration	Oral	Oral	Intravenous	Intravenous	Oral	Oral	Oral
Class	Multi-tyrosine kinase inhibitor	Multi-tyrosine kinase inhibitor	mTOR inhibitor	VEGF inhibitor	mTOR inhibitor	Multi-tyrosine kinase inhibitor	Tyrosine kinase inhibitor
Recommended Dose	400mg orally twice daily, without food	50mg orally once daily, with or without food, 4 weeks on treatment, 2 weeks off treatment	25mg infused over a 30- to 60-minute period, once a week	10mg/kg infused over 90 minutes every 2 weeks; IFN-α – 9 million IU SQ 3 times a week	10mg orally once daily at the same time every day, with or without food	800 mg orally once daily, without food	5mg orally twice daily (may increase dose to 7mg, then 10mg every 2 consecutive weeks)

*Only related to renal cell carcinoma **aRCC**=advanced renal cell carcinoma **mRCC**=metastatic renal cell carcinoma

Table 2 **Drug Regimens and Costs**

Drug	Cost per Dose/ Infusion[a]	Number of Doses/Infusions per 28 Days	Drug Cost per 28-Day Cycle[b]	Total Cost per 28-Day Cycle
Nexavar (sorafenib)	$175.41	56	$9,823.20	$9,823.20
Sutent (sunitinib malate)	$423.74	28	$7,909.75[c]	$7,909.75
Torisel (temsirolimus)	$1,405.10[d]	4	$5,620.40[d]	$5,620.40[d]
Avastin (bevacizumab)	$4,543.98[d]	2	$9,087.96[d]	$11,322.12[d,e]
Interferon–alfa-2b	$186.18	12	$2,234.16	
Afinitor (everolimus)	$326.44	28	$9,140.38	$9,140.38
Votrient (pazopanib)	$256.69	28	$7,187.39	$7,187.39
Inlyta (axitinib)	$162.05	56	$9,074.96	$9,074.96

a. See Table 1 (page 31) for recommended dosing. For oral products, cost is based on the number of units required per dose and the number of doses needed per day. Weight-based dosing for bevacizumab is calculated for a 70kg individual.
b. Costs based on wholesale acquisition cost (WAC).
c. The dosing for Sutent is 28 days on, 14 days off. To account for this, the average cost per 28 days was identified.
d. Cost is not including administration fees.
e. Cost of combination therapy is based on recommended use.

efficacy compared to placebo. Unfortunately, due to the scarcity of comparative research, superiority has not been established between first- and second-line therapies in either of the two histologies. These factors make it difficult to develop a streamlined treatment pathway that demonstrates the greatest likelihood of positive patient outcomes.

Treatment of aRCC is personalized to the patient's response to therapy. In targeted therapies, treatment failure is a common aspect that can help guide clinicians in therapy choice. Treatment failure is defined as progression of disease, discontinuation due to intolerable side effects, or death. A common case of progression is the mutation of the tyrosine kinase receptors. This causes the current TKI therapy to lose effectiveness and the need for subsequent therapies. For patients progressing after responding to initial therapy, the use of structurally different TKIs may be appropriate second- or even third-line therapy, as these agents may remain effective against the mutated receptors. For this reason, physicians may sequence multiple TKIs before switching to a new mechanism of action. In patients who do not respond to TKI therapy, usually defined as treatment failure within six months of therapy, mTOR inhibitors may be considered as second- or third-line therapy, to slow or inhibit the progression of disease. Bevacizumab with IFN-α is indicated as a first-line therapy, but IFN-α has a less tolerable side effect profile compared to TKI and mTOR inhibitors.

It is important to remember that many patients will be appropriate candidates for—and able to tolerate—multiple lines of therapy. It is not uncommon for a patient to receive four or even five trials of different medications throughout the course of his or her treatment. Therefore, in addition to first- and second-line treatment options, contingencies may need to be considered to allow access to subsequent therapies in appropriate patients.

Pharmacoeconomic Considerations

While safety and efficacy should be the most important pharmacologic considerations when reviewing oncology treatment options, the rapidly increasing costs of these medications are also of concern to healthcare payors. Managed care organizations (MCOs) are tasked with handling the financial strain associated with the addition of new targeted therapies for advanced and relapsed cancers. The primary goal is to provide access to the most therapeutically appropriate products while controlling the rise in expenditure. Previously, the lack of therapeutic options left aRCC relatively unmanaged by MCOs. However, with the addition of seven targeted therapies in the last nine years for the treatment of aRCC, MCOs are entertaining the option of implementing a more structured management approach as a strategy to promote positive outcomes and limit unnecessary spending.

One of these strategies includes optimizing cost-effective therapies, especially in treatment-naïve patients. Most patients will be going through a sequence of therapies due to treatment failure; however, the lack of treatment consistency creates challenges when attempting to predict cost and associated

outcomes. To help streamline the treatment process, some organizations are beginning to develop more structured management approaches, including clinical pathways of care. In addition to potential cost-saving advantages, this structure can help to reduce treatment inconsistencies between practices while also allowing for the appropriate individualization of therapy.

With a crowded pharmacologic pipeline, the RCC treatment paradigm is likely to evolve with the approval of additional—and expensive—targeted therapies. Although

Figure 1: Treatment Algorithm for mRCC per NCCN Guidelines[3]

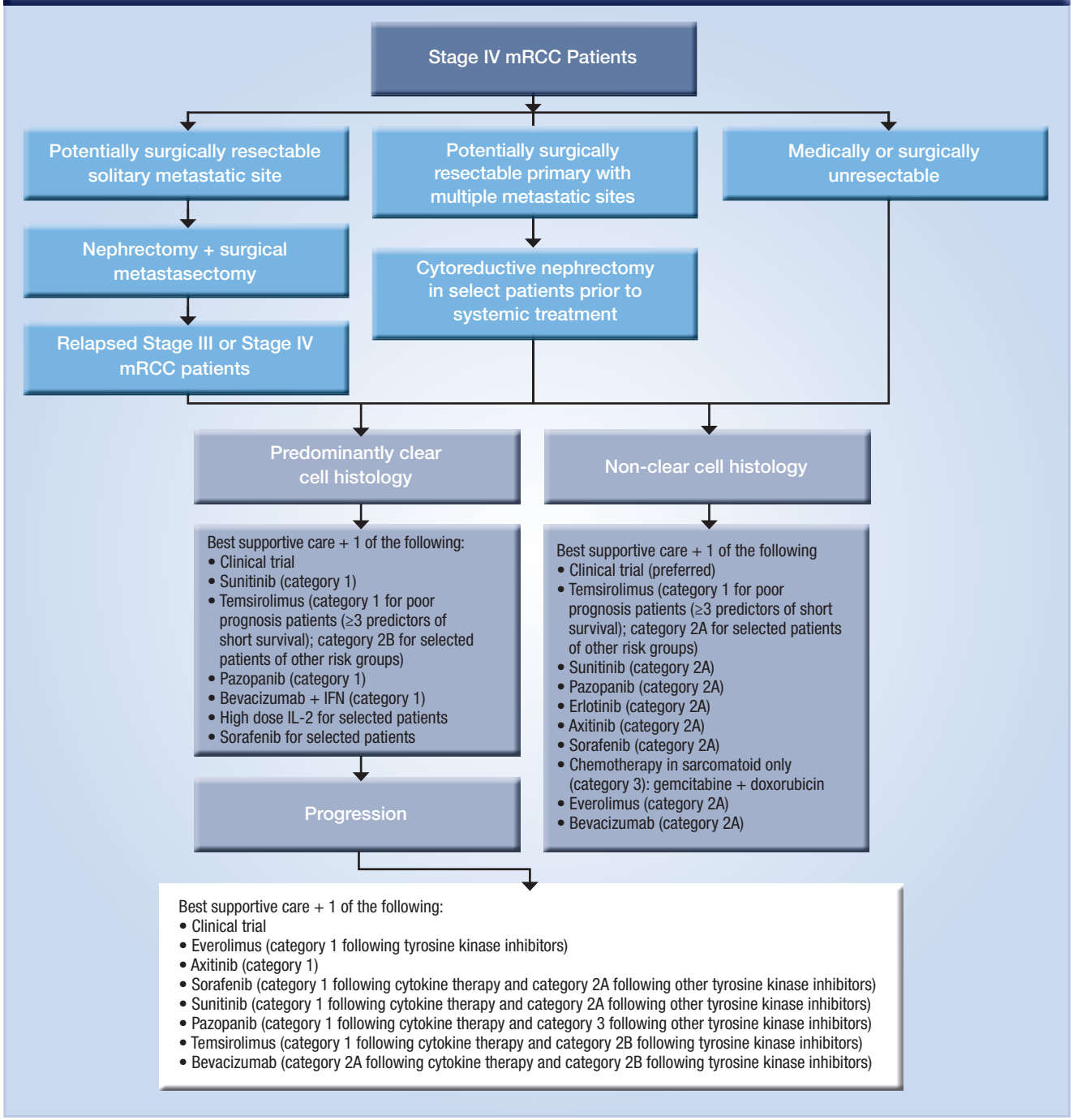


Table 3 Phase III Clinical Outcomes for mRCC Drug Therapy[3]

CLINICAL OUTCOMES

VEGF-Pathway Inhibitors	Sunitinib (Sutent)–Pfizer	
Patient Population	First-line systemic therapy for patients with metastatic RCC	
	Sunitinib N=375	Interferon-alfa N=375
Median PFS (Months)	11	5
P-value (PFS)	<0.001	
Hazard Ratio (PFS)	0.42	
Median OS (Months)	26.4	21.8
P-value (OS)	0.051	
Hazard Ratio (OS)	0.821	

VEGF-Pathway Inhibitors	Axitinib (Inlyta)–Pfizer	
Patient Population	In patients with mRCC following failure of 1 prior systemic first-line therapy	
	Axitinib N=361	Sorafenib N=362
Median PFS (Months)	6.7	4.7
P-value (PFS)	<0.0001	
Hazard Ratio (PFS)	0.665	
Median OS (Months)	20.1	19.2
P-value (OS)	0.3744	
Hazard Ratio (OS)	0.969	

VEGF-Pathway Inhibitors	Sorafenib (Nexavar)–Bayer/Onyx	
Patient Population	In patients with mRCC following failure of one prior systemic first-line therapy	
	Sorafenib N=384	Placebo N=385
Median PFS (Months)	5.5	2.8
P-value (PFS)	<.01	
Hazard Ratio (PFS)	0.44	
Median OS (Months)	17.8	15.2
P-value (OS)	0.146	
Hazard Ratio (OS)	0.88	

VEGF-Pathway Inhibitors	Bevacizumab (IV) (Avastin)–Genentech	
Patient Population	Treatment-naïve mRCC in post-nephrectomy	
	Bevacizumab + IFN alfa 2a N=327	Placebo + IFN alfa 2a N=322
Median PFS (Months)	10.2	5.4
P-value (PFS)	<0.001	
Hazard Ratio (PFS)	0.63	
Median OS (Months)	23.0	21.0
P-value (OS)	0.1291	
Hazard Ratio (OS)	0.86	

VEGF-Pathway Inhibitors	Pazopanib (Votrient)–GSK	
Patient Population	Patients who had received no prior systemic therapy for locally advanced or metastatic RCC of clear cell histology	
	Pazopanib N=557	Sunitinib N=553
Median PFS (Months)	8.4	9.5
P-value (PFS)	Met noninferiority criteria	
Hazard Ratio (PFS)	1.047	
Median OS (Months)	28.4	29.3
P-value (OS)	0.275	
Hazard Ratio (OS)	0.908	
Patient Population	Patients with advanced and/or mRCC with a diagnosis of clear-cell or predominately clear-cell histology	
	Pazopanib N=290	Placebo N=145
Median PFS (Months)	9.2	4.2
P-value (PFS)	<0.0001	
Hazard Ratio (PFS)	0.46	
Median OS (Months)	22.9	20.5
P-value (OS)	0.224	
Hazard Ratio (OS)	0.91	

mTOR Inhibitors	Temsirolimus (IV) (Torisel)–Pfizer	
Patient Population	Untreated patients with mRCC	
	Temsirolimus N=209	IFN alfa N=207
Median PFS (Months)	5.5	3.1
P-value (PFS)	0.0001	
Hazard Ratio (PFS)	0.66	
Median OS (Months)	10.9	7.3
P-value (OS)	0.0078	
Hazard Ratio (OS)	0.73	

mTOR Inhibitors	Everolimus (Afinitor)–Novartis	
Patient Population	Patients with mRCC whose disease progressed despite prior treatment with sunitinib, sorafenib, or both sequentially	
	Everolimus N=277	Placebo N=139
Median PFS (Months)	4.9	1.9
P-value (PFS)	<0.0001	
Hazard Ratio (PFS)	0.33	
Median OS (Months)	N/A	

allowing open access to oncology products is typically the preferred management strategy among payors, with the expense associated with treating this population expected to further increase, new management strategies may need to be explored to keep the financial impact sustainable.

Another important consideration is the histology of RCC. Up to 70 percent of RCC cases are of clear-cell histology and, as a result, studies of the various treatment options involve mostly or only these patients.[3] This limits the category 1 recommendations for non-clear cell patients to temsirolimus and enrollment in clinical trials. All patients with aRCC should be counseled on palliative care options, such as surgery, bisphosphonates, radiation, and optimal pain management. In patients opting for palliative care, quality of life should be optimized with symptom control.

Based on the NCCN guidelines for the treatment of aRCC, there are five first-line targeted therapies available. These include sunitinib, temsirolimus, bevacizumab and IFN-2α, pazopanib, and sorafenib for selected patients.[3] From a cost perspective, non-orally administered drugs would include added fees of weekly infusions for temsirolimus, bimonthly infusions for bevacizumab, and three times per week subcutaneous injections for IFN-2α. Infusion prices fluctuate depending on site of care (e.g., physician's offices, homecare agencies, or hospital-based infusion centers), and the two products that are affected by increased costs are temsirolimus and bevacizumab. Cost can be minimized by utilizing infusion centers. Side effects of these drugs, such as GI perforation for bevacizumab and hypersensitivity reactions for temserolimus, warrant the need for patients to receive treatment in an office or institutional setting, instead of homecare. All other therapies are orally administered daily or twice daily.

Clinical trials have recently been conducted to aid in appropriately sequencing the therapies. The phase III COMPARZ trial demonstrated non-inferiority of pazopanib compared to sunitinib in terms of progression-free survival in clear-cell RCC.[9] In addition, 11 of the 14 quality-of-life categories were significantly improved in the pazopanib arm of the study. This is significant when considered in conjunction with the phase III PISCES trial. This trial assessed the tolerability and safety of pazopanib and sunitinib with a focus on patient preference.[10] After adjusting for sequence, 70 percent of patients reported preferring treatment with pazopanib, 22 percent preferred sunitinib, and 8 percent had no preference ($p<0.001$). Secondary outcomes showed that physicians also preferred pazopanib and fewer patients discontinued treatment prematurely.

Second-line therapies include axitinib and everolimus, as well as any of the other listed first-line therapies. Bevacizumab with IFN-α is also indicated for use in patients who have failed first-line treatment, but is rarely used as a second-line option. Finally, joining clinical trials may be the preferred option for aRCC patients, particularly those with non-clear cell histology. In addition, cost may be minimized by adhering to the prescribing information and using the approved supportive care medications for specific drugs. This could prevent or minimize the risk for hypersensitivity reactions or other complications. Other cost considerations include medications to alleviate side effects such as nausea, hypertension, and hemorrhage.[11]

In patients with a metastatic or progressive cancer, it is important to factor in quality of life. Targeted therapy can deliver higher quality of life because of prolonged progression-free survival and tolerable side effect profiles. Though targeted therapy is now the mainstay of aRCC, the most cost-effective choice of agents remains unclear. As additional comparative research is completed, more structured treatment guidelines should be developed and published that address not only first-line, but also second- and third-line therapies.[12] The development of evidence-based treatment protocols, in conjunction with physician input, can ensure a consistent level of care for all patients and allow healthcare payors to more accurately predict the financial impact of treating this patient population.

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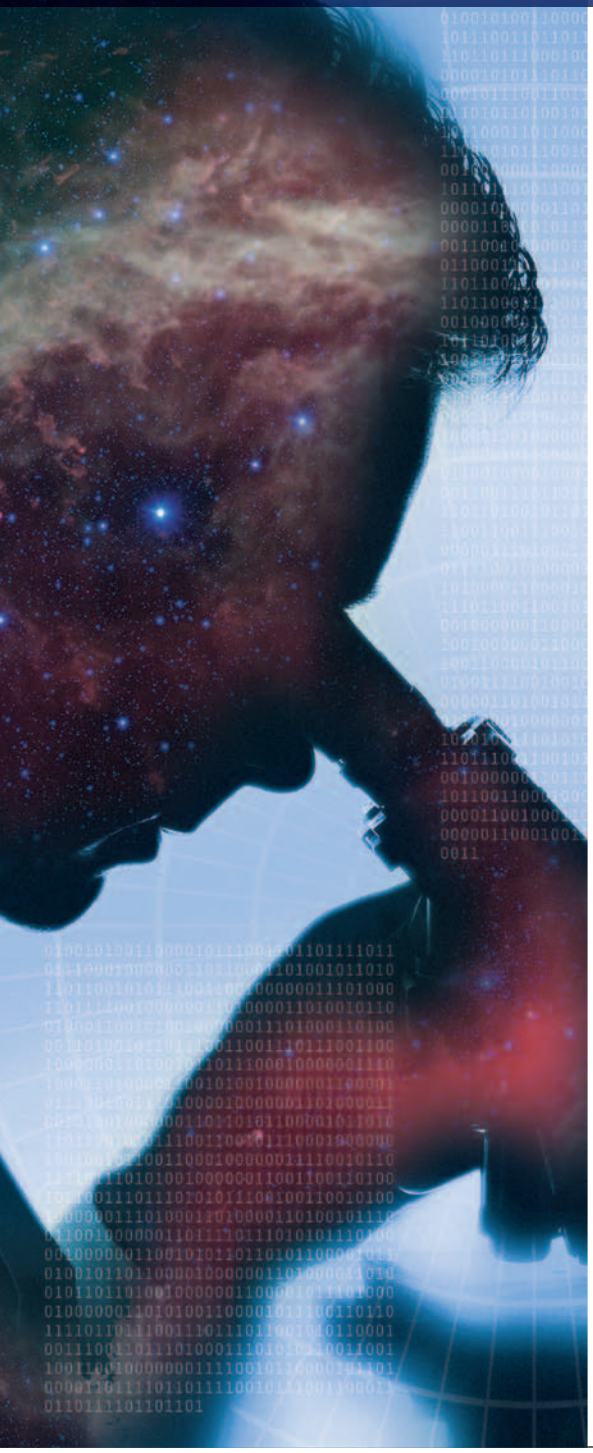
Needles are sold separately and may require a prescription in some states.

Levemir® FlexPen®
insulin detemir (rDNA origin) injection

September 2013

Integration of Medical and Pharmacy Benefits at the Health Plan Level

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



Matthew Mitchell, PharmD

Integrated healthcare is a topic that, while not new to the industry, has recently been coming to the forefront. In conjunction with healthcare reform, many organizations are seeking to integrate, or further integrate, medical and pharmacy benefits.[1] Integrated benefit management holds the promise of several positive results, including improving quality of care, improved care coordination—particularly around transitions in care—and possible improved patient outcomes while controlling costs.[1,2]

Integrated data can be used by payors to create a more complete overall assessment of treatment for plan members.[1,3] Claims may be submitted via medical or pharmacy benefit; not analyzing these benefits together may result in an incomplete understanding of the patient population and medical/pharmacy utilization.[1,3,4] The integrated data can help payors identify gaps in treatment that can be targeted to help improve patient outcomes.[1-3] In addition, integrated assessment of medical and pharmacy benefits is necessary to perceive a complete accounting of the total cost of care.[3-5]

Integration of benefits is of particular interest in conditions that require treatment in which specialty drugs have become a standard of care.[1,3,5] Included in this are rheumatoid arthritis (RA), multiple sclerosis (MS) and oncology, where claims may be split between the two benefit designations.[3-5]

Integrated Care

Fully integrated care involves the physicians, pharmacists, and payors working together to provide the best care for the patient.[1] Integration is key to improving and maintaining quality healthcare.[6] In order to achieve this, programs and communication channels must be in place so that information regarding the patient can be shared in a way that will optimize treatment.[1,7] This applies not just in the short term, for making treatment decisions, but in the long term, where integrated patient information can be tracked to determine if meaningful health outcomes have been achieved.[1]

Specialty Drug Conditions

Conditions such as RA and MS—in addition to oncology—which utilize specialty drugs and contribute significantly to claims expenditures, are of particular interest for integration of benefits.[1,3,5] Specialty medications may be covered

under pharmacy or medical benefits, such as for drugs that require intravenous infusion in physicians' offices, hospitals, or clinics.[4,5] The total cost of care for RA patients is greater among those patients utilizing specialty medications and is increasing annually, particularly due to increased usage and price increases of specialty drugs.[4,5] As with RA, many MS patients require specialty medications that may be covered under either benefit.[5,8,9] Treatment costs for MS are expensive, more so than for RA.[5,10] One study calculated that one out of every 40 pharmacy benefit dollars is spent on 82.2 claims per 100,000 members per month.[10] Specialty medical and pharmacy drug costs may exceed half of the total cost of care for these patients.[5,8] In addition, the cost of specialty MS medications has been consistently rising and at a larger inflation rate than for many other prescription medications.[5,8-11] Oncology treatment costs are high, with expenditures, including those for specialty drug products, increasing more rapidly than in other areas.[12] Antineoplastic treatments may be divided between benefits, with oral chemotherapeutic agents covered under pharmacy benefit and intravenously administered agents, antiemetics, and other medications covered under medical benefit.[1,12]

Cost-Effectiveness and Closing the Gaps in Care

One application of integrated benefits is identifying where gaps in care exist for plan members.[1,2] Gaps in care can include over- or underuse on the medical or pharmacy side, as well as patient safety monitoring.[2] One focus area may be medication adherence.[2,9] While increased adherence to specialty medications, such as for RA and MS, may prove more costly in the short run, the long-term benefits of adherence may contribute to meaningful health and economic outcomes.[5,13]

In patients suffering from specialty disease states, both the clinical and financial split between benefits makes these patients difficult to manage from a health plan perspective.[7] However, the expertise that managing specialty drugs requires is becoming increasingly cost-effective to bring in-house through integration.[6] By integrating benefits, payors will be able to better monitor therapy, compliance, and total costs.[7] With any of these specialty drug conditions, treatment outcomes can be identified quickly through analysis of the integrated data.[1] Integrated benefits can allow for comparative treatment effectiveness, improved coordination of care, and monitoring for adverse events.[1,14,15] Monitoring for events such as hospitalizations, or lack thereof, can indicate whether treatment should be continued or if an intervention is needed.[1] One way monitoring can be accomplished in oncology is by using complete blood count or other laboratory results to check for response markers or cytopenias, which can be indicative of adverse reactions. Payors can also indicate the need for assessments or blood work at pre-specified intervals and can then follow up directly with practitioners to ensure that these assessments have been completed.[1] Payors can then act upon these results and intervene on the patient's behalf—for example, to help stop unnecessary or harmful treatments, as in cases of treatment failure or adverse events.[1,2] One study found that integrated benefits resulted in fewer adverse events, while groups with separate pharmacy benefits had a 7 percent higher rate of hospitalizations, which correlated to an estimated $9.15 per member per month (pmpm) cost difference.[15] Another study found that integration resulted in a 19 percent lower rate of hospitalizations and a 28.6 percent lower rate of emergency room visits, correlating to $19.76 pmpm medical cost-savings.[16]

Integrated medical and pharmacy benefits can result in an average of 2.7 to 7.5 percent cost-savings on medical care.[15-17] A cost-savings of $0.53 pmpm has been observed among patients with RA as well, and with other conditions that rely heavily on pharmacotherapy and chronic medications (Table 1, page 40).[15,16] Care and case management programs, which provide a way to set treatment goals and monitor outcomes, have been shown to reduce MS exacerbations and hospitalizations.[7]

Payors can also use the integrated data to better identify patients who could benefit from disease management and education programs.[7,15,17] Integrated benefit management will allow for a more accurate identification of this population, as opposed to pharmacy claims only, in which the disease state is inferred.[18] These programs can be used to monitor and reduce adverse drug interactions, monitor and manage controlled substance usage, off-label usage and polypharmacy, and help coordinate patient care, especially in complex cases.[2,5,13,17] The programs can also be used to identify and target gaps in care, such as the need for behavioral health support.[7,17] Multidisciplinary teams can more efficiently and proactively work together and with the plan members under an integrated model. Nurses and clinical pharmacists can proactively assess patient motivation/readiness to change, help identify gaps in care, safety concerns, and compliance issues, and work with the patients, the provider(s), and other team members to implement action plans. The clinical team, including phar-

Table 1 Cost-Savings for Conditions with Chronic Medication Treatment for Members with Integrated versus Non-Integrated Benefits

Condition	Percent Medical Cost-Savings per Patient from 2008-2010[16]	3-Year Average Cost-Savings per Patient from 2008-2010[16]	Cost-Savings per Member per Month from 2007-2008[15]
Mood disorders	NA	NA	$1.58
Asthma	0.5%	-$2.01	$0.80
Diabetes	3.3%	$20.47	$0.59
Hypertension	NA	NA	$0.24
CAD	2.8%	-$27.12	NA
CHF	19.3%	$286.68	NA
COPD	5.6%	$43.68	NA
RA	NA	NA	$0.53

Key: CAD=Coronary artery disease; **CHF**=Congestive heart failure; **COPD**=Chronic obstructive pulmonary disease; **NA**=Not available; **RA**=Rheumatoid arthritis

macists, will have access to case management information and lab results, which will assist in medication counseling and patient-centered care.[13] Program information or cost-saving opportunities can be relayed directly to the members by a customer service representative supporting both benefits.[13,15] Patients may also be triaged directly to a case manager who will be able to answer questions and provide information and support.[13]

Payors can also implement tools to help members with integrated benefits. Online pricing tools that will allow members to compare brands and generics while including tiers, mail order discounts, and other factors can significantly assist with conversion to generics and result in drug cost-savings.[6] Specialty drug supply can also benefit from integration. Mail order services may be brought in-house under an integrated model and payors can better provide a reliable source of specialty drugs.[6,7,13] Members will benefit from not only improved outcomes, but also from an improved experience, and payors will be able to help control costs via optimal treatment management.[1,15]

Integrated benefits can allow for preferred pathway options to be developed by payors in collaboration with practitioners and to guide placement of prior authorizations (PAs) and utilization management policies.[5,12] Longitudinal integrated health information can also assist in the creation of treatment protocols based on clinical results.[1] In addition, many plans are shifting specialty drug coverage to be solely under the pharmacy benefit, which will help ensure correct and safe drug utilization. This will also aid in minimizing erroneous billing while increasing transparency.[5,7,12] However, lack of integrated data can result in delayed, incomplete, or incorrect benefit assessments, particularly as the processing and adjudication of medical claims may occur at different times than pharmacy claims.[2,12] Data on total cost of care may also be incomplete and may hamper the ability to detect fraud and abuse.[12,14] As such, there may be limitations or delays in creating benefit designs.[12] Integrated data will allow payors to more clearly see how total treatment costs are divided between community-based medical and pharmacy services and clinical, diagnostic, imaging, and other hospital-based services.[14] As a result, payors may see improvements in Centers for Medicare & Medicaid (CMS) Star Ratings or an increase in related bonus payments.[2]

Healthcare Reform, Health Information Technology, and Accountable Care Organizations

With healthcare reform implementation gaining momentum, new care models and payor arrangements are being designed and put into practice.[19] Of particular interest is the development of Accountable Care Organizations (ACOs), which is encouraged by the Affordable Care Act (ACA).[1] The integrated care provided via ACOs, and the ACO-payor relationship, has the potential to increase quality of care while controlling costs.[1,9,19] Use of health information technology (HIT) is a way for payors and ACOs to help achieve these outcomes.[18,19] Data collected from ACOs or disease management programs, with the assistance of HIT, will allow payors and ACOs to share

and analyze information, conduct comparative effectiveness analyses, and make evidence-based decisions.[1,6,9,18] Ultimately, the goal is to optimize treatment via utilization of these methods.[1]

HIT can be used to help identify target populations of patients who would benefit from intervention.[6] This can also be applied to an analysis of historical claims data. Risk-sharing plans can then be created via development of population health models and predictive models can forecast disease-specific individual member risk.[6,19] In addition, technology such as electronic medical records (EMRs) and management software will allow integration of care and communication between payors and practitioners.[14,19] Payors can provide real-time pharmacy claims information via HIT to medical providers at the point of care.[20] Automated messages and alerts can be sent via HIT to practitioners at the time of order entry or via EMR.[2] EMR information can also assist payors in creating and adjusting coverage policies, including determining the most cost-effective method for drug supply delivery and channel to the most cost-effective site of care.[14]

HIT can also be used to monitor patient care and drug usage, such as in cases of long-term oncology treatment, and manage chronic diseases.[6] Real-time reports and alerts can be generated, which can be communicated between payors and practitioners within the ACOs to help make treatment decisions.[1,6,12] Actions can be implemented via programs such as mediation therapy management (MTM) to help close the gaps in care and improve patient outcomes.[18] Payors can further integrate care management by bringing disease management in-house. Enrolling patients in an in-house integrated program can also result in cost-savings and lower medical costs.[6]

Editorial assistance provided by Daria I. Grisanzio, PharmD

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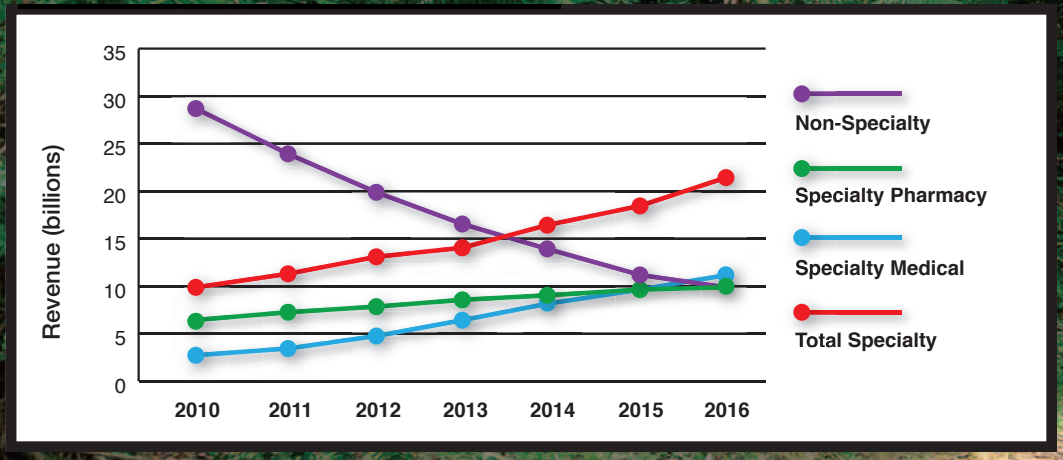

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PIPELINE TRENDS

NEW DRUG APPROVALS			
Drug	**Manufacturer**	**Approval Date**	**Indication**
Adempas® (riociguat) tablet	Bayer	October 8, 2013	Soluble guanylate cyclase (sGC) stimulator for the treatment of pulmonary hypertension
Otrexup™ (methotrexate) injection	Antares	October 11, 2013	Folate analog metabolic inhibitor for use in the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriasis
Novoeight® (turoctocog alfa) injection	Novo Nordisk	October 15, 2013	Antihemophilic factor (recombinant) indicated for use in adults and children with hemophilia A
Opsumit® (macitentan) tablet	Actelion	October 18, 2013	Dual endothelin receptor antagonist for the treatment of patients with pulmonary arterial hypertension
Zohydro™ ER (hydrocodone) capsule	Zogenix	October 25, 2013	Opioid analgesic for around-the-clock management of moderate to severe chronic pain
Gazyva™ (obinutuzumab) injection	Genentech	November 1, 2013	CD20-directed cytolytic antibody used in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia
Imbruvica™ (ibrutinib) capsule	Janssen	November 13, 2013	Bruton's tyrosine kinase (BTK) inhibitor for treatment of mantle cell lymphoma
Olysio™ (simeprevir) capsule	Janssen	November 22, 2013	Protease inhibitor for the treatment of chronic hepatitis C infection
Sovaldi™ (sofosbuvir) tablet	Gilead	December 6, 2013	Oral nucleotide analogue for treatment of chronic hepatitis C virus (HCV)
Anoro™ Ellipta™ (umeclidinium bromide and vilanterol) inhalation powder	GlaxoSmithKline	December 18, 2013	Once daily LAMA/LABA combination for the treatment of COPD
Orenitram™ (treprostinil) tablets	United Therapeutics Corporation	December 20, 2013	Oral prostacyclin for the treatment of pulmonary arterial hypertension
Tretten® (coagulation factor XIII A-subunit) injection	Novo Nordisk	December 23, 2013	Recombinant analogue of human Factor XIII A-subunit for prevention of bleeding in patients with congenital Factor XIII A-subunit deficiency
Farxiga™ (dapagliflozin) tablet	Bristol-Myers Squibb and AstraZeneca	January 8, 2014	Selective sodium-glucose cotransporter-2 inhibitor for treatment of adults with type 2 diabetes
Hetlioz™ (tasimelteon) capsule	Vanda Pharmaceuticals	January 31, 2014	Melatonin receptor agonist for treatment of non-24-hour disorder in the totally blind

Disclosures: The information contained in Pipeline Trends is current as of February 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**
Abraxane® (paclitaxel)	September 6, 2013	Expanded approval for treatment of late-stage pancreatic cancer
Stelara® (ustekinumab)	September 20, 2013	Approved to treat active psoriatic arthritis
Cimzia® (certolizumab)	September 27, 2013	Approved for treatment of active psoriatic arthritis
Perjeta®(pertuzumab)	September 30, 2013	Approved for treatment of neoadjuvant breast cancer
Cimzia® (certolizumab)	October 17, 2013	Approved for the treatment of adults with active ankylosing spondylitis
Nexavar® (sorafenib)	November 22, 2013	Approved to treat metastatic differentiated thyroid cancer
Mekinist™ (trametinib)	January 9, 2014	Approved for use in combination with dabrafenib for treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations

NEW FORMULATIONS AND DOSAGE FORMS		
Drug	**Approval Date**	**Advertised Advantage**
Actemra® (tocilizumab) injection	October 21, 2013	Subcutaneous formulation approved for use in adult patients with moderately to severely active rheumatoid arthritis
Noxafil® (posaconazole) tablet	November 25, 2013	Now available in a delayed-release tablet with less frequent dosing
Copaxone® (glatiramer acetate) injection	January 28, 2014	40mg/mL glatiramer injection approved for 3-times-a-week dosing

NEW FIRST-TIME GENERIC DRUG APPROVALS
Capecitabine (Xeloda®) tablet: Approved September 16, 2013
Paricalcitol (Zemplar®) capsule: Approved September 27, 2013
Esomeprazole/naproxen (Vimovo®) tablet: Approved September 27, 2013
Clonidine (Kapvay®) extended-release tablet: Approved September 30, 2013
Tobramycin (Tobi®) inhalation solution: Approved October 10, 2013
Diclofenac (Solaraze®) topical gel: Approved October 28, 2013
Abacavir/lamivudine/zidovudine (Trizivir®) tablet: Approved December 5, 2013
Duloxetine (Cymbalta®) capsule: Approved December 11, 2013
Telmisartan (Micardis®) tablet: Approved January 8, 2014
Telmisartan/Amlodipine (Twynsta®) tablet: Approved January 8, 2014
Sirolimus (Rapamune®) tablet: Approved January 8, 2014
Sunitinib (Sutent®) capsule: Approved January 30, 2014

NEW GENERATION OF CHRONIC HCV TREATMENT

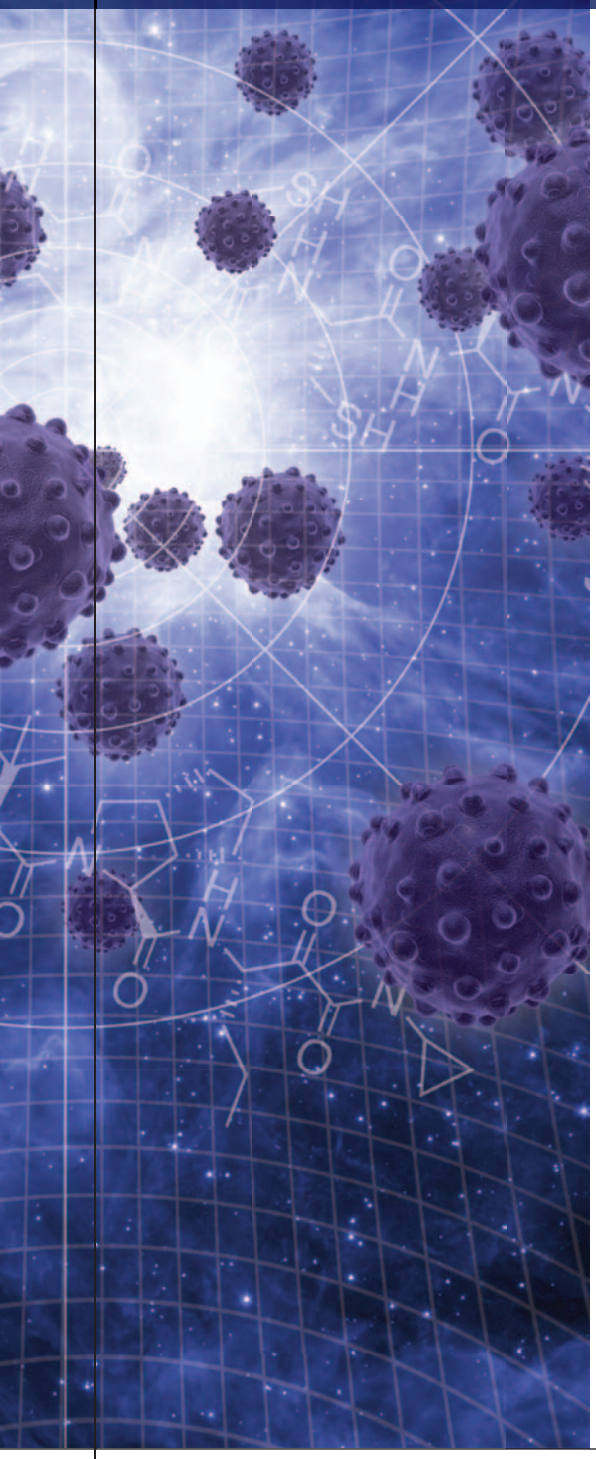
Janssen's Olysio™ and Gilead's Sovaldi™ are the two latest treatment options to be approved by the FDA for the treatment of genotype 1 chronic HCV in combination with Peg-IFN and ribavirin. While offering more convenient, once-daily dosing, they come at a price comparable to or higher than their predecessors, Incivek® and Victrelis®. An entirely Peg-IFN-free treatment regimen for genotype 1 will likely not be seen until 2015.

Drug	Manufacturer	MOA	WAC
Incivek (telaprevir)	Vertex	Protease Inhibitor	$22,052 (168ct)
Olysio (simeprevir)	Janssen	Protease Inhibitor	$22,120 (28ct)
Sovaldi (sofosbuvir)	Gilead	Nucleotide Analog Inhibitor	$28,000 (28ct)
Victrelis (boceprevir)	Merck	Protease Inhibitor	$6,687 (336ct)

Genotype 1 Treatment Cost		
Drug Therapy	**Treatment Duration**	**Cost**
Incivek + Peg-IFN + ribavirin	24 weeks (12I, 24P, 24r)	$85,460
	48 weeks (12I, 48P, 48r)	$104,765
Victrelis + Peg-IFN + ribavirin	28 weeks (24V, 28P, 28r)	$62,643
	36 weeks (32V, 36P, 36r)	$82,451
	48 weeks (32V, 48P, 48r)	$92,103
	48 weeks (44V, 48P, 48r)	$112,164
Olysio + Peg-IFN + ribavirin	24 weeks (12O, 24P, 24r)	$85,665
	48 weeks (12O, 48P, 24r)	$104,970
Sovaldi + Peg-IFN + ribavirin	12 weeks (12S, 12P, 12r)	$93,653
Sovaldi + ribavirin*	24 weeks (24S, 24r)	$170,381

*Indicated only for patients who are ineligible for interferon-based therapy.
Peg-IFN pricing based on Peg-Intron WAC $705.19/unit; ribavirin pricing based on 200mg tablet WAC $2.36/unit.

HCV Landscape Update and Managed Care FAQs



In 2011, health plan expenditures associated with hepatitis C virus (HCV) drastically increased following U.S. Food and Drug Administration (FDA) approval of two protease inhibitors, Incivek® and Victrelis®. These products, in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV), were quickly recognized as the gold standard of treatment for genotype 1 HCV.[1] Although these triple-drug regimens were able to demonstrate significant improvements in clinical outcomes, they greatly increased HCV-related costs for health plans. Not only did the protease inhibitors increase the cost of treatment per patient, but patient "warehousing" by physicians led to a large number of newly treated patients and further escalated the costs following the availability of these products. In 2013, the wave of HCV expenditures began to subside with the anticipation of new HCV therapies approaching FDA approval. Physicians had once again begun delaying treatment in patients with HCV until new, and potentially more effective, therapies became available.

Two of these highly anticipated therapies were approved by the FDA within the last six weeks of 2013, Olysio and Sovaldi. Olysio is the third protease inhibitor approved to treat HCV, but offers some benefits that may separate it from the previously approved products. Indicated only for genotype 1 patients, Olysio should be taken once daily with food for 12 weeks as part of a 24- to 48-week combination with Peg-IFN and RBV.[2] Before initiating a patient on Olysio, it is important to screen for an NS3 Q80K polymorphism. Olysio was determined to be less effective for these patients in clinical trials.[2]

Sovaldi belongs to a new HCV drug class called nucleotide analog inhibitors and is indicated for HCV genotypes 1, 2, and 3.[3] Sovaldi should be taken once daily for 12 weeks with Peg-IFN and RBV for genotype 1, and for 12 to 24 weeks with RBV for genotypes 2 and 3.[3] Although no head-to-head trials have been conducted, clinical trials with Sovaldi have resulted in SVR rates higher than those seen in protease inhibitor trials. In fact, the American Association for the Study of Liver Diseases (AASLD) now recommends Sovaldi in combination with Peg-IFN and RBV as the treatment of choice for treatment-naïve patients. However, cost will be an important consideration for managed care executives, as Sovaldi is $1,000 per day, a cost that exceeds the other products that are currently available.[4]

With several additional products in the near-term pipeline, including interferon-free options from Abbott, Gilead, and Boehringer Ingelheim, the HCV market is expected to become crowded and exponentially more expensive for managed care organizations. However, it is important to consider the "cost per cure" when assessing the true value of new-to-market HCV products. Although these new regimens carry a substantial up-front cost, their simplicity, tolerability, and efficacy will hopefully increase the proportion of patients completing therapy, reduce the likelihood of viral resistance, and minimize wasted health plan resources, resulting in enhanced patient outcomes and cure rates.

Figure 1: HCV Annual Cost Trend[5]

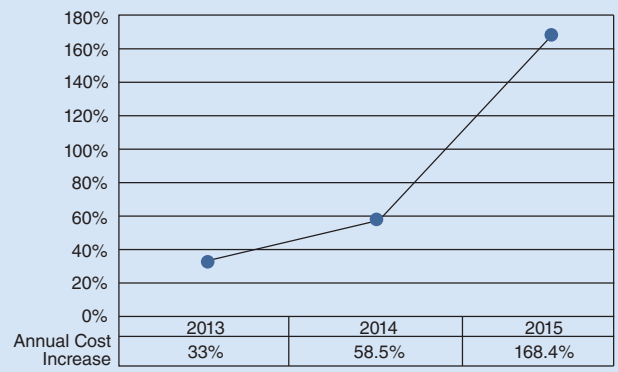


Table 1 — Oral Chronic HCV Therapies[2-4,6,7]

Drug	Sovaldi (sofosbuvir)	Olysio (simeprevir)	Incivek (telaprevir)	Victrelis (boceprevir)
Manufacturer	Gilead	Janssen	Vertex	Merck
Mechanism of Action	Nucleotide analog inhibitor	Protease inhibitor		
Dosing	400mg oral tablet once daily	150mg oral capsule once daily	(3) 375mg oral tablets (1,125mg) 2 times daily	(4) 200mg oral capsules (800mg) 3 times daily
Administration	With or without food	With any type of food	With 21gm fat/ dose	With light snack/ meal
Indication	Chronic HCV Genotypes 1,4: + Peg-IFN + RBV; Genotypes 2,3: + RBV only	Chronic HCV genotype 1 in combination with Peg-IFN + RBV		
Patient Population	Genotypes 1,2,3,4	Genotype 1 with compensated liver disease		
Treatment-Naïve SVR Response	Genotypes 1,4: 90% Genotype 2,3: 93-97%	Genotype 1: 80%	Genotype 1: 72-79%	Genotype 1: 63-66%
Treatment-Experienced SVR Response	Genotype 1: Not available Genotype 2: 82-90% Genotype 3: 77%	Genotype 1: 53% (null) 65% (partial) 77-79% (relapse)	Genotype 1: 32% (null) 59% (partial) 86% (relapse)	Genotype 1: 38% (null) 40-52% (partial) 70-75% (relapse)
Duration of Therapy	Genotypes 1,2,4: 12 weeks Genotype 1 Peg-IFN ineligible: 24 weeks Genotype 3: 24 weeks	12 weeks of simeprevir; 24-48 weeks total treatment	12 weeks of telaprevir; 24-48 weeks total treatment	24-44 weeks of boceprevir; 28-48 weeks total treatment
Common Adverse Effects	Fatigue, headache, nausea, insomnia, and anemia	Rash (including photosensitivity), pruritus, and nausea	Rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus	Fatigue, anemia, nausea, headache, and dysgeusia
WAC (4 weeks of therapy)	$28,000	$22,120	$22,052	$6,687

Table 2 Genotype 1 Treatment Regimens for Olysio and Sovaldi[2,3]

Olysio (Simeprevir) Treatment Schedule

	0	STOP 4	STOP 12	STOP 24	48	Total Cost
Treatment-naïve and prior relapsers	Simeprevir-12					$85,665
	Peg-IFN + ribavirin-24					
Prior partial or null responders	Simeprevir-12					$104,970
	Peg-IFN + ribavirin-24					

Stop therapy at week 4 or week 12 if HCV-RNA ≥25 IU/mL.
Stop Peg-IFN and Ribavirin at week 24 if HCV-RNA ≥25 IU/mL.

Sofosbuvir Treatment Schedule

	0	12	24	Total Cost
All patients	Sofosbuvir-12			$93,653
	Peg-IFN + ribavirin-24			
Patients ineligible for Interferon-based regimen	Sofosbuvir-24			$170,381
	Ribavirin-24			

No futility rules are included in the Sovaldi prescribing information.

Table 3 Treatment Cost for Treatment-Naïve HCV Genotype 1[2-4,6,7]

Drug Therapy	Treatment Duration	Cost
Incivek® + Peg-IFN + ribavirin	24 weeks (12I, 24P, 24r)	$85,460
	48 weeks* (12I, 48P, 48r)	$104,765
Victrelis® + Peg-IFN + ribavirin	28 weeks (24V, 28P, 28r)	$62,643
	48 weeks* (32V, 48P, 48r)	$92,103
Olysio™ + Peg-IFN + ribavirin	24 weeks (12O, 24P, 24r)	$85,665
Sovaldi™ + Peg-IFN + ribavirin	12 weeks (12S, 12P, 12r)	$93,653
Sovaldi™ + ribavirin**	24 weeks (24S, 24r)	$170,381

*Extended treatment durations are indicated for patients with detectable HCV RNA early into therapy.
**This interferon-free regimen is indicated only in patients who are interferon-ineligible.

Peg-IFN pricing is based on Peg-Intron WAC $705.19/unit; ribavirin pricing is based on 200 mg tablets WAC $2.36/unit.

Frequently Asked Questions and Answers:

Should genotype 1a patients be screened for NS3 Q80K polymorphism before starting Olysio?

Yes. In clinical trials, Olysio was substantially less effective in genotype 1a patients with the NS3 Q80K polymorphism.[2] The prescribing information recommends that alternative therapy should be considered for these patients.[2] Payors can avoid waste by requiring screening prior to initiation of therapy.

If a genotype 1a patient has an NS3 Q80K polymorphism, should he or she stay away from all PIs?

No, the other protease inhibitors are not known to be less effective in these patients, and the prescribing information for Victrelis and Incivek does not suggest alternative therapy as it does with Olysio.[2,6,7]

Can IL28B genotyping be used as a substitute for NS3 Q80K screening?

No. Although the IL28B CC genotype can be a positive predictor for successful HCV therapy, any genotype 1a patient with the NS3 Q80K polymorphism is expected to have a reduced response to Olysio and alternative therapy should be considered.[2]

If a patient failed Incivek or Victrelis, could he or she try Olysio or Sovaldi?

Similar to Incivek and Victrelis, the efficacy of Olysio has not been studied in patients who have previously failed therapy with a treatment regimen that contains a protease inhibitor.[2] However, since Sovaldi is in a different drug class and thus utilizes a different mechanism of action,[3] Sovaldi may be considered as a treatment option for patients who have previously failed therapy with a protease inhibitor.

Can Olysio and Sovaldi be used together in an interferon-free regimen?

A phase IIa trial (COSMOS) studied the use of Olysio and Sovaldi in combination for genotype 1 patients who were prior null responders to Peg-IFN and RBV therapy.[8] The trial yielded optimistic results with SVR rates above 90 percent both with and without RBV.[8] Although this combination of agents is not currently approved by the FDA, it is the recommended initial therapy for genotype 1 patients who are not eligible to receive IFN by the AASLD.

Are there futility rules for Sovaldi?

No, unlike the protease inhibitors, there are no futility rules recommended in the Sovaldi prescribing information.[3] However, strict monitoring of adherence remains extremely important.

Can patients who have previously failed or relapsed from Peg-IFN and RBV start Sovaldi in combination with Peg-IFN and RBV?

Yes. As long as the patient does not have a contraindication to Peg-IFN or RBV (or experienced a severe adverse reaction during previous therapy), Sovaldi triple therapy is an appropriate treatment option for patients who have either failed or relapsed from previous Peg-IFN and RBV treatment.[3]

Can Sovaldi be used without Peg-IFN in genotype 1 patients?

Sovaldi plus RBV without Peg-IFN can be considered for patients who are interferon-ineligible.[3] However, the indicated duration of therapy is twice as long (24 weeks) in this regimen compared to the Peg-IFN-containing combination.[3] It may benefit payors to strictly define interferon "ineligible" and maximize the utilization of the standard regimen.

Should Olysio patients be required to have HCV RNA levels drawn at week 4 before therapy authorization is extended?

The futility rules for Olysio begin at week 4.[2] Therefore, it would be appropriate to have HCV RNA levels drawn at that point in therapy. To prevent waste due to unnecessary drug spending, payors may want to consider implementing a requirement to have the RNA levels drawn prior to extending the authorization of therapy to 12 weeks.

When will there be an all-oral therapy for all genotype 1 patients?

Multiple pharmaceutical manufacturers are expected to file with the FDA in 2014, and approvals of interferon-free regimens in genotype 1 patients could come as soon as late 2014 or early 2015.

References

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

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

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. 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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Version: 6

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

Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924, 7,235,627, 8,114,833 and other patents pending. Victoza® Pen is covered by US Patent Nos. 6,004,297, RE 43,834, RE 41,956 and other patents pending.

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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