Fall 2013

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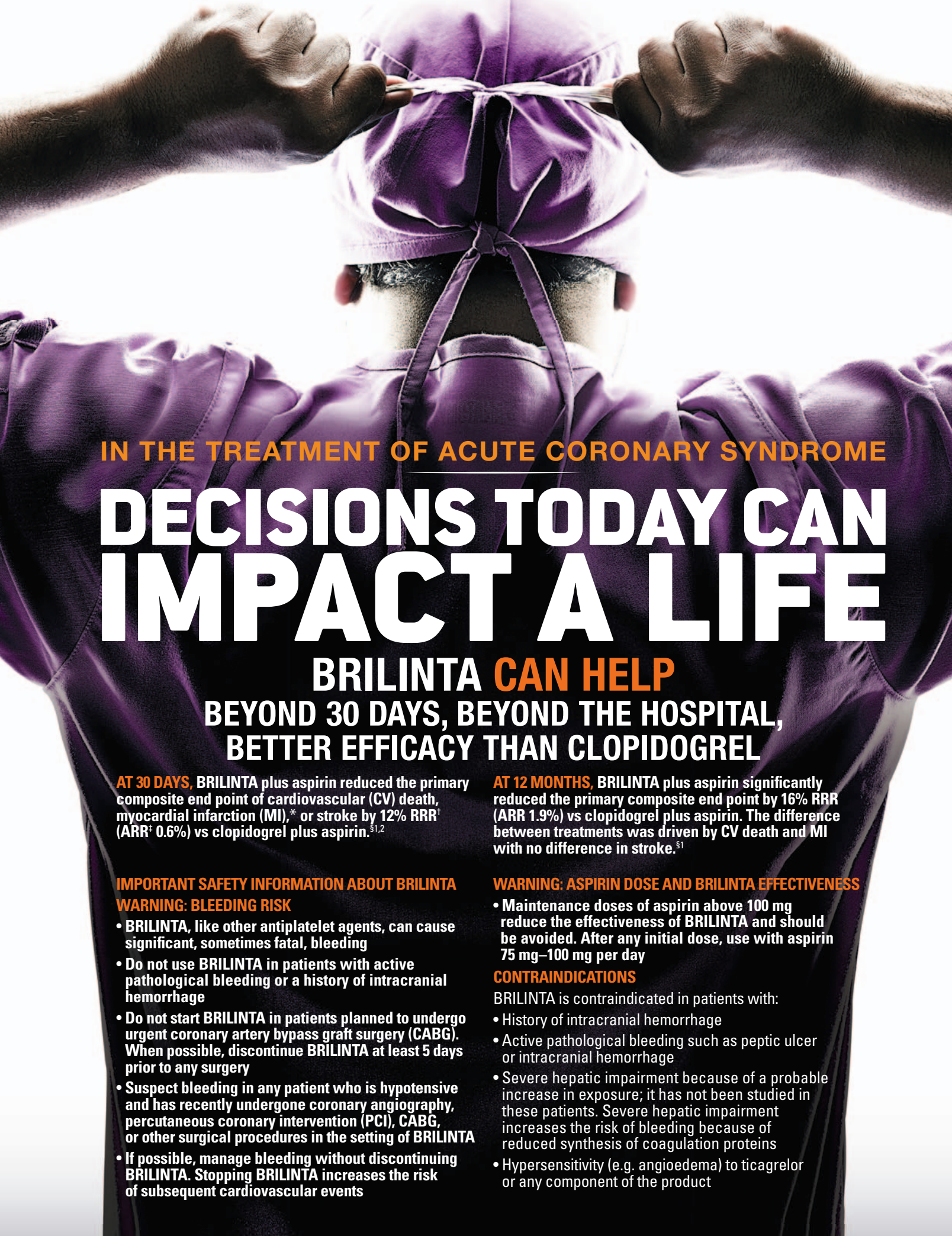


IN THE TREATMENT OF ACUTE CORONARY SYNDROME

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]

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

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

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

AstraZeneca

BRILINTA® *(ticagrelor)* Tablets

WARNING: 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*]

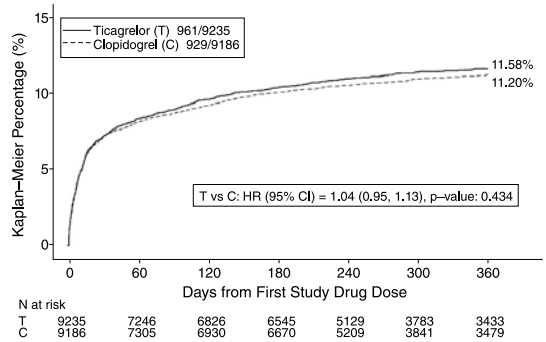
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety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

to this issue

features

trends

Letter from the President

Susan Petrovas

Dear Managed Care Colleagues,

Susan Petrovas, RPh, President

CDMI is committed to improving clinical and economic outcomes for our health plan customers. As part of this commitment, managing the continually increasing cost of specialty pharmaceuticals is a primary focus for CDMI. One of the more recent additions to our Specialty Management Solutions is in the oncology marketplace. With the explosion of FDA-approved oral oncology agents, ensuring appropriate utilization in a cost-conscious manner is more important than ever.

In addition to our focus on oncology initiatives, CDMI offers a variety of formulary management options that can be customized based on plan-specific needs and can be applied to both the pharmacy and medical benefits. In addition to multiple sclerosis, rheumatoid arthritis, and hepatitis C, CDMI provides formulary management solutions for categories such as Gaucher disease, hereditary angioedema, infertility, neurotoxins, oral oncology, and others. In addition, CDMI can help health plans better understand their medical pharmacy utilization and identify key trends and opportunities to improve cost-conscious care.

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

As always, CDMI continues to offers a wide variety of clinical programs that complement many of our formulary management solutions. These programs are designed to improve adherence/persistency, coordination of care, site-of-care optimization, and outcomes for our clients' beneficiaries. Each program is developed in tandem with key opinion leaders in their respective fields to ensure compliance with 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 you may have. Thank you for reading!

Sincerely,

Susan C. Petrovas, RPh
President, CDMI

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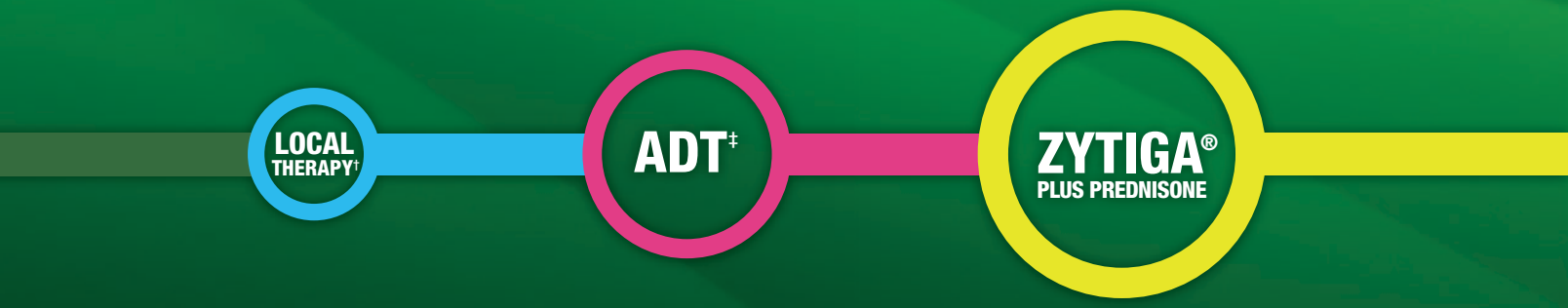

For more information, please visit **www.zytigahcp.com**.

IMPORTANT SAFETY INFORMATION

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

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

ZYTIGA® Next

5.2 Months

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

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

57% Reduction

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

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

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

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

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

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

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

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

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

K08Z12176

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

†Local therapy = radiation and/or surgery.

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

§Primary endpoint.

‖Secondary endpoint.

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

Janssen Biotech, Inc.

3/13 K08Z13049

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

Table 1: Adverse Reactions due to ZYTIGA in Study 1

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

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

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

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

Table 2: Laboratory Abnormalities of Interest in Study 1

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

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

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

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

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

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

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

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

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

[1]Based on non-fasting blood draws

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

OVERDOSAGE

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

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

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

ZYTIGA® (abiraterone acetate) Tablets

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

Manufactured by:
Patheon Inc.
Mississauga, Canada

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

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MANAGED CARE NEWSSTAND

FDA Approves New Treatment Option for Patients with Hemophilia B

The U.S. Food and Drug Administration (FDA) approved Rixubis (coagulation factor IX [recombinant]) for use in patients ages 16 and older who have hemophilia B. The drug is used for routine treatment to prevent or reduce the frequency of bleeding, to control bleeding episodes, and for perioperative management of symptoms. Rixubis is the first new drug of its type approved in more than 15 years for this type of hemophilia.

"As the first recombinant coagulation factor IX indicated specifically for routine prophylaxis to prevent bleeding, Rixubis becomes a new weapon in our arsenal to protect hemophilia B patients," said Karen Midthun, MD, Director of the FDA's Center for Biologics Evaluation and Research, in a news release.

The FDA approval follows a Phase I/III study evaluating the effectiveness of using Rixubis twice a week for six months. The study found the median annualized bleeding rate was 2.0; 43 percent of patients had no bleeds.

This medication represents a new option that may help physicians and patients reduce bleeding episodes and better manage this chronic disease.

Source: U.S. Food and Drug Administration. FDA approves first recombinant coagulation factor IX that is specifically indicated for routine use in preventing bleeding episodes (prophylaxis). Accessed 5 Sept. 2013 at **www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm358918.htm**.

One in Two RA Patients Discontinues Biologic Medication in the First Two Years

About one-third of patients with rheumatoid arthritis (RA) stop or change therapy during the first year of treatment, and half stop treatment within two years, according to researchers who presented their findings at EULAR 2013, the Annual Congress of the European League Against Rheumatism. The reasons given for stopping treatment included loss of efficacy (35.8 percent), physician preference (27.8 percent), safety (20.1 percent), and patient preference (17.9 percent).

The researchers gathered information about RA patients from the U.S. Consortium of Rheumatology Researchers of North America (CORRONA) database. More than 6,000 patients met the criteria for inclusion in the study.

The researchers noted that the rates of and reasons for discontinuation of treatment were similar whether patients were taking tumor necrosis factor inhibitors (TNFi) or non-TNFi biologics.

This study highlights the importance of monitoring RA patients closely during the first years of treatment to help manage symptoms and prevent and/or reduce permanent joint damage.

Source: Strand V, et al. Discontinuation of biologic therapy in rheumatoid arthritis (RA): Analysis from the Consortium of Rheumatology Researchers of North America (CORRONA) database. Annual Congress of the European League Against Rheumatism. June 2013.

New Blood Thinner May Be Effective and Safer than Conventional Therapies

Physicians may have a new option to help prevent blood clots in patients at risk for acute venous thromboembolism. A study in the *New England Journal of Medicine* found that the drug Eliquis® (apixaban) helps prevent dangerous blood clots in the legs and lungs as well as standard therapy does, but with less risk for major bleeding.

The researchers compared the use of apixaban with traditional treatment (subcutaneous enoxaparin, followed with warfarin) in 5,395 patients with acute venous thromboembolism. Apixaban was as effective as conventional treatment and was associated with a 69 percent reduction in major bleeding.

The researchers say that apixaban may be a simple, effective, and safe drug for initial and long-term treatment of acute venous thromboembolism.

Source: Agnelli G, et al. Oral apixaban for the treatment of acute venous thromboembolism. *NEJM*. DOI: 10.1056/NEJMoa1302507. 1 July 2013.

Use of Expensive Treatments Rising in Men with Low-Risk Prostate Cancer

More men with low-risk prostate cancer are undergoing expensive, advanced treatments, such as robotic prostatectomy and intensity-modulated radiotherapy, even when they are unlikely to see benefits from these treatments.

Researchers compared the use of advanced technologies with prior standard treatments, such as external beam radiation treatment, open radical prostatectomy, and observation, in men at low risk of dying from prostate cancer. They found that the use of advanced therapies increased dramatically from 2004 to 2009 in men with low-risk prostate cancer, those at greater risk of dying from something other than prostate cancer, and those who had both a low-risk prostate cancer and a high risk of dying from something other than cancer.

The researchers concluded that "continued efforts to differentiate indolent from aggressive disease and to improve the prediction of patient life expectancy may help reduce the use of advanced treatment technologies in this patient population."

Source: Jacobs B, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *JAMA*. June 2013;309(24):2587-2595.

Study Confirms Long-Term Benefit of Intensive Therapy for Type 1 Diabetes

Aggressive, long-term therapy for patients with Type 1 Diabetes Mellitus (T1DM) can help them reach blood glucose levels that are near normal and significantly reduce their risk for diabetes-related complications, such as diminished kidney function, severe eye disease, stroke, and heart disease.

Researchers reported the results of a 30-year National Institutes of Health-funded diabetes study. Twenty years ago, study investigators reported that intensive therapy reduced early stages of diabetes-related complications by as much as 76 percent. Intensive therapy included frequent insulin injections or insulin pump therapy and frequent patient self-monitoring of blood sugar levels with finger-stick testing. Based on those findings, intensive therapy for T1DM became the standard of care.

Now, researchers report that patients with T1DM who were treated with intensive therapy for many years experienced a variety of benefits, such as a 50 percent reduction in their risk for impaired kidney function, a nearly 60 percent reduction in heart disease and stroke, and a 50 percent reduction in vision-threatening eye disease.

These findings emphasize the importance of helping diabetic patients gain control over their blood glucose levels.

Source: American Diabetes Association. Major long-term benefits of intensive therapy for type 1 diabetes: Study reports near-normal glucose levels lead to large reductions in kidney, heart, severe eye diseases and stroke. Press Release. 22 June 2013.

New Study to Evaluate Recombinant Factor VIII Compound in Children with Hemophilia A

Bayer HealthCare has started enrolling patients in an international Phase II/III trial to evaluate the effectiveness of using BAY94-9027 as prophylaxis in male children with hemophilia A. BAY94-9027 is a recombinant human factor VIII (rFVIII). As part of the study, the compound is being used at least once a week and as needed for acute bleeding episodes.

The study will enroll 50 previously treated patients up to the age of 12 who have severe hemophilia A and a history of at least 50 exposure days with any FVIII product. The researchers will assess a variety of outcome measures, including annualized bleeding episodes, pharmacokinetics, and the effect of treatment on acute bleeding episodes and adverse events.

This study in children will complement the company's ongoing research using this compound in adults.

Source: Bayer HealthCare Pharmaceuticals, Inc. Bayer initiates phase III trial of an investigational recombinant factor VIII compound in children with hemophilia A. Press Release. 9 July 2013.

Optimizing the Value of Targeted Therapy in the Growing CML Patient Population

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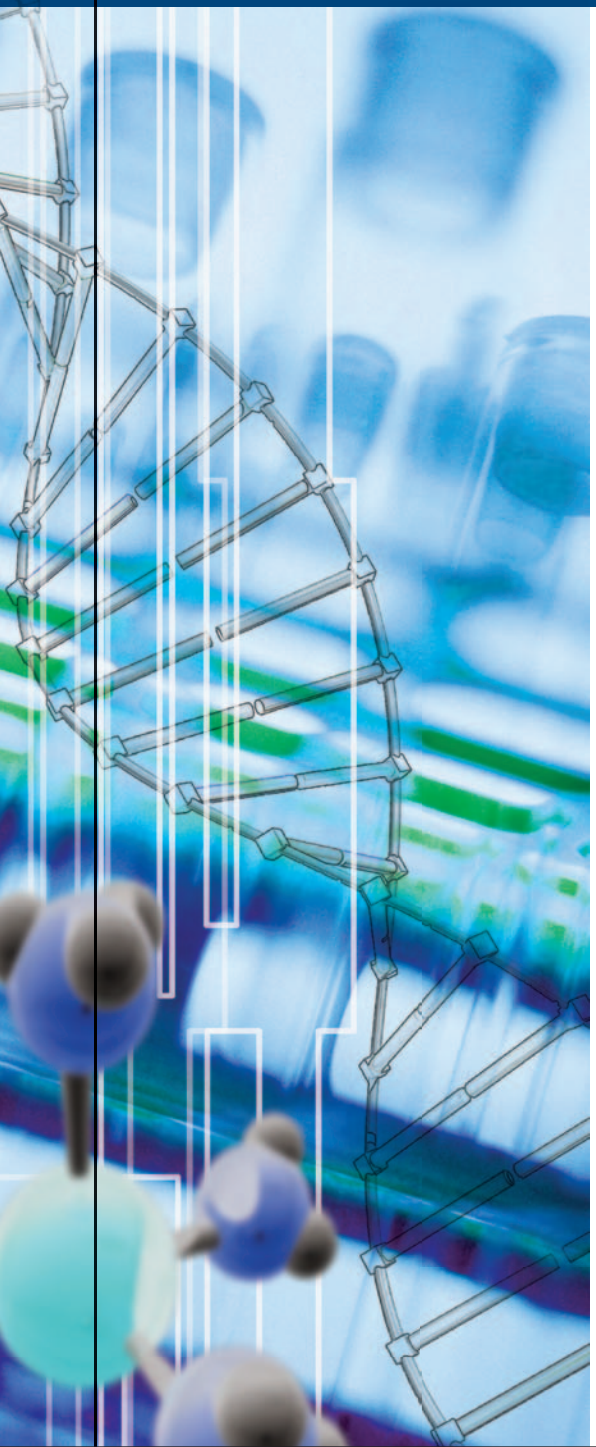


Stuart L. Goldberg, MD

Chronic myelogenous leukemia (CML) is a rare myeloproliferative neoplasm that serves as a model for understanding the impact of a successful but expensive cancer treatment. Although CML accounted for only 12 percent of all new leukemia cases in the United States last year, with approximately 6,000 new patients, the prevalence of CML has grown dramatically, from less than 30,000 cases prior to 2000 to approximately 80,000 current cases. This prevalence is expected to double over the next 20 years.[1,2] The rise is due primarily to improved outcomes associated with tyrosine kinase inhibitor (TKI) therapies, which have turned this once uniformly fatal disease (barring transplantation therapy) into a chronic disorder, with projected 10-year survival rates exceeding 80 percent.

Although the TKI products are extending survival in patients with CML, the optimization of pharmacological approaches in the course of daily practice remains a concern. Furthermore, the increased utilization of TKIs (which averages >$100,000/year) presents financial challenges in a market in which costs have already become difficult to control.[3,4] To address these challenges, managed care organizations (MCOs) are searching for new strategies to help contain the escalating cost of cancer care while also providing high-quality healthcare to their beneficiaries. A rational first step in this process is to optimize the use of the most clinically effective medications based on patient-specific responses to therapy. These efforts will need to include appropriate selection of first-line and salvage TKI products, widespread adoption of appropriate monitoring of response to therapy with course corrections, and strategies to encourage patient adherence to oral TKI therapies over extended time frames.

CML and Disease Progression

CML is a progressive hematologic malignancy in which bone marrow stem cells (BMST) generate malignant myeloid precursor cells, or blasts, without regard to physiological cell growth signals.[5] The proportion of blasts to non-blast cells in the BM places the patient into one of three CML stages: chronic phase (CP), accelerated phase (AP), or blast crisis phase (BP) (See Figure 1). Most patients present in an asymptomatic CP

when they are noted to have increased white blood cells (leukocytosis) or mild enlargement of the spleen during routine medical care. The diagnosis of CML is confirmed when cytogenetic and/or molecular tests from either the BM or peripheral blood detect the Philadelphia (Ph [+]) chromosome or the Ph (+) chromosome's BCR-ABL messenger RNA. The CP is the most responsive stage to oral therapy and is associated with the best outcomes. If left untreated, CML will progress to the more advanced stages of AP or BP over a period of three to five years. In AP or BP patients, an increase in malignant blast cells can lead to bone marrow failure, placing the patient at risk for fatigue (anemia), bleeding (thrombocytopenia), and infections (neutropenia). Therefore, the principle therapeutic goal in CML is to avoid disease progression to the treatment-resistant AP or the treatment-refractory BP through effective, early treatment of the CP.

Pathology Details: The Philadelphia Chromosome and BCR-ABL

The hallmark of CML is the Ph (+) chromosome, which is formed by a reciprocal translocation between the long arms of chromosomes 9 and 22. This results in a new fusion gene (BCR-ABL), which codes for the Bcr-Abl protein (p210). This protein has dysregulated tyrosine kinase activity and is believed to be the key driver of CML disease development. Inhibition of this signaling pathway is the mechanism by which TKIs bring about a decline in disease progression.[6]

The presence of the Ph (+) chromosome or the BCR-ABL messenger RNA in samples of bone marrow or peripheral blood may serve as a useful biomarker of disease activity. Experience dating back 20 years with interferon therapy demonstrated that persistent suppression of the Ph (+) chromosome measured on serial bone marrow evaluations correlated with decreased rates of progression from CP to the advanced phases of the disease. Patients who were able to achieve a complete cytogenetic response (CCyR), as evidenced by no Ph (+) positive metaphases on a 20 metaphase bone marrow karyotype specimen, enjoyed prolonged survival.[7] Subsequently, peripheral blood monitoring of BCR-ABL messenger RNA using polymerase chain reaction (PCR) technology (molecular monitoring) has become commonplace and has facilitated standardized treatment algorithms based on time-dependent milestones for response.

Oral TKI Choices in CP-CML

The National Comprehensive Cancer Network (NCCN) has published, and continues to update, a series of guidelines for the management of patients with CML.[8] The NCCN guidelines emphasize that initial therapy choice

Figure 1: Staging CML: Chronic Phase (CP); Accelerated Phase (AP); Blast Phase (BP)

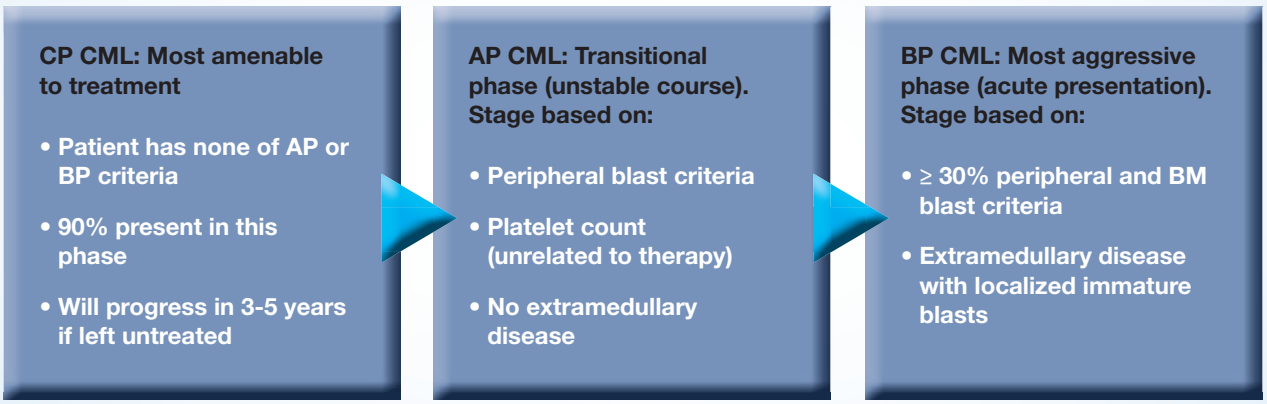


Table 1 Oral Tyrosine Kinase Inhibitors Indicated for the Treatment of CML

		Gleevec® (imatinib) Novartis – 1st Generation	Sprycel® (dasatinib) BMS Squibb – 2nd Generation	Tasigna® (nilotinib) Novartis – 2nd Generation	Bosulif® (bosutinib) Pfizer – 2nd Generation	Iclusig® (ponatinib) Ariad – 3rd Generation
† Indications		1st line: CP, AP, BP	1st line: CP 2nd line: Any phase	1st line: CP 2nd line: CP or AP	2nd line: Any phase	2nd line: Any phase
‡Dosing Schedule	Initial	400 mg QD	100 mg QD	300 mg BID	*500 mg QD	45 mg QD
	Resistance	600 mg QD	140 mg	400 mg BID	*600 mg QD	45 mg QD
	Directions	Administered with a meal and large glass of water (reduces GI toxicity)	Administered without regard to meals	Must avoid food 2 hours before and 1 hour after administration	Should be taken with meal	Administered without regard to meals
Cost	WAC	$232.36/unit	$286.07/unit	**$286.07/ 4 units	$272.71/unit	$319.33/unit
	Per Year	$83,650	$102,986	$102,986	$98,175	$114,960

Source: U.S. Food and Drug Administration
†FDA-approved indications for use in Ph (+) CML adults
‡Recommended dosing for adults with chronic phase Ph (+) CML

*In the second-line setting, initial means after a TKI failure and resistance means that treatment response is less than optimal by eight to 12 weeks of starting the second-line agent.
**For Tasigna: 150 mg x 4 pills = 300 mg BID

should be influenced by a patient's risk score, sustaining patient compliance (e.g., posology, tolerance) and patient baseline comorbidities. Three TKI products (imatinib, dasatinib, and nilotinib) are FDA approved as initial therapy for CP disease, with two additional agents (bosutinib and ponatinib) approved in salvage settings. Omacexatime, a non-TKI agent administered by subcutaneous injection, has also recently gained FDA approval in the salvage setting.

With the approval of multiple oral agents as first-line therapy, choosing the appropriate TKI to prescribe has become more complicated. Unfortunately, the data evaluating specific differences between the products and efficacy in certain patient populations remains scarce. As a deeper understanding of the CML disease state emerges and more treatment options become available, patient-specific characteristics have become one of the most influential factors in choosing which TKI offers the most cost-effective benefits.

First-Line Setting: Risk Stratification

As part of the initial diagnostic work-up, the practitioner may calculate a risk score to determine the potential effectiveness of TKI therapy and to aid in selection of treatment. The Sokal score assigns patients into low, intermediate, or high-risk categories based on age, splenomegaly, platelet count, and percentage of peripheral blasts. The Hasford score, used more commonly in Europe, adds to these factors the percentage of peripheral eosinophils and basophils. The newly defined European Treatment and Outcome Study (EUTOS) score, using spleen size and basophils only, may be more predictive of outcomes in the TKI era.[9] Studies have shown that there is a relationship between these risk categories at diagnosis and the rate of disease progression; furthermore, the newest data indicates that using second-generation inhibitors as initial therapy offers intermediate-high risk Sokal patients (IHRP) clinical and economic benefits.[10]

Imatinib was the first TKI product FDA approved for front-line therapy of CP Ph (+) chromosome CML

By 2030, the prevalence of CML is projected to more than double, and the costs of newly developed targeted cancer therapies are following a similar pattern. With a thorough understanding of the disease intricacies and judicious incorporation of best-practice guidelines, an expert care plan for members can ensure patient safety and fiscal responsibility.

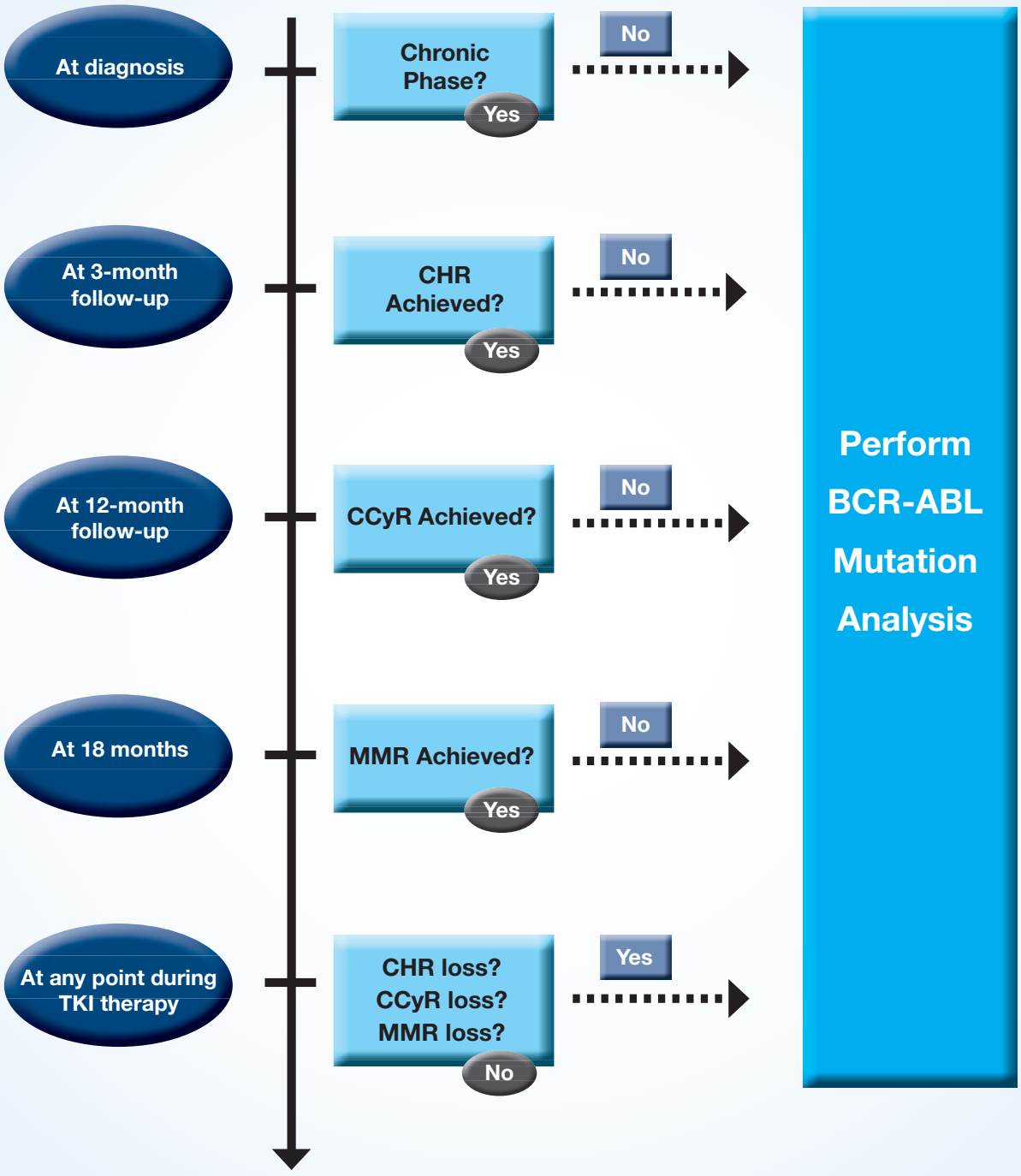
based on the results of the randomized IRIS trial. In this study, more than 70 percent of patients achieved a CCyR at the end of the first year, with the majority of patients still alive at the eight-year follow-up. The agent was well tolerated with few discontinuations for side effects.[11,12] Given more than a decade's experience, imatinib at a dose of 400 mg daily remains the most commonly prescribed initial therapy. High-dose imatinib (800 mg) as front-line therapy was not found to be beneficial, as it resulted in similar cytogenetic remission rates, but yielded increased toxicities. Thus, the role of high-dose imatinib is discouraged by the NCCN.[13] Imatinib is the least expensive TKI; the cost differential is expected to widen within the next two years as generic versions of imatinib become available.

Dasatinib and nilotinib were both FDA approved, in 2006 and 2007 respectively, as salvage approaches for patients who were resistant or intolerant to imatinib therapy. In 2010, the results of two randomized phase III comparison trials (ENESTnd and DASISION) both documented superior one-year rates of cytogenetic and molecular responses for these second-generation agents, compared to imatinib as initial therapy.[14,15] Based on the early surrogate end points, these TKI products were FDA approved for front-line use. However, as of three years follow-up, neither study has documented a survival benefit for the newer TKI product. In both studies, however, the majority of patients progressing to AP/BP on the imatinib arm had intermediate- or high-risk Sokal scores at diagnosis. Additionally, the three-month molecular response rates in the intermediate/high Sokal risk cohorts, felt to be predictive of long-term survival, were superior with the second-generation products. Thus, the NCCN guidelines recommend the second-generation TKI products for the 30 to 40 percent of newly diagnosed CML patients with unfavorable Sokal risk scores.[8]

Monitoring Therapeutic Response

Early identification of non-adherence, non-responsiveness, or drug resistance gives patients' the best chance of clinical improvement and reduces the risk of unnecessary cost burdens. Oncologists may monitor three surrogate biomarkers, found in the blood and BM, to periodically assess the effectiveness of TKI therapy. Critical therapeutic milestones are met when the assessment, performed at the recommended time periods, demonstrates a decline in disease progression or sustains the evidence of disease arrest. Furthermore, not meeting these essential therapeutic milestones requires a comprehensive patient assessment, including adherence and mutational analyses.[16] If a patient is deemed to have been adherent to his or her TKI therapy, a mutational investigation is required to determine the cause of pharmacologic resistance. The results of this analysis also assist in choosing the most effective salvage TKI therapy. Response monitoring is an effective mechanism for directing therapeutic adjustments toward the most advantageous medication and offers the MCOs justification that the benefit is worth the additional cost of changing therapy. Unfortunately, a recent analysis of two large administrative claims databases identifying more than 1,200 new CP CML patients noted that only approximately one-quarter underwent the appropriate molecular monitoring determined by published guidelines. The analysis demonstrated that patients who underwent three to four PCR tests during the first year of therapy (per NCCN guidelines) incurred 44 percent ($p<0.001$) fewer inpatient (IP) admissions than

Figure 2: NCCN Recommendations for Mutational Analysis



Source: Adapted from **http://bloodjournal.hematologylibrary.org/content/118/5/1208.full.** Accessed 6 Sept. 2013.

patients not undergoing molecular monitoring. Adjusted all-cause IP cost was $5,663 (p=0.005) lower for the three to four tests cohort compared to the zero tests cohort, as was adjusted progression-related IP cost (savings $4,132 [p=0.013]) and adjusted medical service cost (savings $5,997 [p=0.049]).[17] Thus, efforts to increase physician adherence to monitoring guidelines by MCOs could represent not only a cost beneficial strategy, but also a clinical benefit for its members.

Hematologic Response Monitoring

The initial diagnostic evaluation in CML includes a peripheral blood count that serves as the baseline for monitoring the hematologic response (HR) to TKI therapy. A complete HR (CHR) by the three-month mark, evidenced by a normal blood count and complete resolution of palpable splenomegaly, is the most common and only acceptable result of TKI therapy. Fortunately, more than 98 percent of CML patients achieve this milestone. However, it should be noted that a CHR alone is not sufficient to predict prolonged survival.

Cytogenetic Response Monitoring

Early cytogenetic response (CyR) to TKI therapy, by contrast, corresponds to improved survival outcomes. Monitoring for changes in the proportions of BM cells containing Ph (+) chromosomes gives the provider an indication of disease sensitivity to the chosen TKI. Any quantitative reduction in the proportion of Ph (+) cells to normal cells from baseline is defined as a CyR. A patient is termed "responding" if he or she meets or exceeds minimum expectations for CyR at different time points after TKI initiation. Obtainment of a complete cytogenetic response (CCyR) defined as the absence of Ph+ metaphases on a 20-cell preparation has been the gold standard in clinical registration trials with TKIs, as long-term experience has demonstrated that those patients who achieve this degree of tumor suppression have prolonged survival. The loss of CCyR has also been a consistent indication for change in therapy (e.g., a patient who reverts to a positive Ph+ cytogenetic status, having previously been negative).[8,16]

Molecular Response Monitoring

Molecular monitoring, which can be performed on peripheral blood, thus obviating the need for painful and costly bone marrow cytogenetic studies, has emerged as the principle means of following a patient's progress. The quantitative polymerase chain reaction (qPCR), at a cost of approximately $200 to 250 per test, can demonstrate a patient's response (i.e., tumor clearance) or relapse (i.e., tumor reappearance) through amplification of BCR-ABL transcripts, which are quantified for comparison against an International Standard (IS).[18] The NCCN guidelines recommend molecular monitoring every three months until a CCyR is achieved and maintained for three years, at which time the frequency may be reduced to one test every six months indefinitely. The results of this test are reported in terms of log reductions, wherein each log reduction represents a tenfold reduction in the number of RNA transcripts. At untreated baseline, the average patient qPCR value was defined as 100 percent IS (using samples obtained in the original IRIS study). A two-log reduction roughly correlates with a bone marrow CCyR, a level correlating with prolonged survival. A three-log reduction has been termed a major molecular response (MMR), a level of residual cancer in which clinical relapses rarely occur. A 4 to 4.5 log reduction is the new gold standard for eligibility in discontinuation studies.[19] Unfortunately, wide adoption of the International Scale (IS) methodology by academic and commercial laboratories has been slow, restricting comparisons of results between laboratories (i.e., results in non-IS laboratories vary dramatically and thus patient results cannot be followed serially if the samples are changed from one lab to another). Furthermore, as noted above, despite clinical and economic value to molecular monitoring, the majority of patients in the United States are not currently receiving studies per published guidelines.

Resistance, Mutational Analysis, and Adherence

A lack of optimal response at the milestone time points can be due to multiple factors, but resistance, intolerance, and non-adherence are the common causes for treatment failure.[20] Point mutations of the BCR-ABL gene are the most common cause of TKI resistance and can be identified on blood or marrow specimens. The NCCN guidelines recommend a mutational analysis when evidence suggests that the patient is taking the medication as prescribed (e.g., adherent and tolerant) but still not meeting the critical response milestones.[8] The identification of a mutation supports a diagnosis of resistance and identifies a subset of patients at higher risk for clinical disease progression. Mutational studies are also potentially helpful in selecting salvage TKI strategies, as the various mutations demonstrate different sensitivities to TKI products. For example, a patient who has acquired a T315I mutation would be predicted

Table 2 NCCN Recommendations on Selecting Salvage Products Based on Mutational Results

Mutation	Treatment Options
T315I	Ponatinib (preferred), omacetaxine, stem cell transplant, clinical trial
V299L	Consider ponatinib, nilotinib or omacetaxine
T315A	Consider ponatinib, nilotinib, imatinib, bosutinib, or omacetaxine
F317L/V/I/C	Consider ponatinib, nilotinib, bosutinib, or omacetaxine
Y253H, E255K/V, F359V/C/I	Consider ponatinib, dasatinib, bosutinib, or omacetaxine
Any other mutation	Consider ponatinib, high-dose imatinib, dasatinib, nilotinib, bosutinib, or omacetaxine

Source: Adapted from **http://bloodjournal.hematologylibrary.org/content/118/5/1208.full**.

to be sensitive to ponatinib, but not to any of the other TKI agents. Given the cost of the mutational test versus subjecting a patient to an expensive ineffective treatment, the performance of a mutational study prior to starting salvage therapy is a very cost-effective measure. Figure 2 (page 20) illustrates the NCCN recommendations for obtaining a mutational study. Table 2 illustrates selecting a salvage TKI product based on mutational analysis.

CP-CML patients will demonstrate primary resistance 25 percent of the time and secondary resistance an estimated 8 percent of the time after two years on imatinib therapy. Patients who fail to achieve the three-month hematologic milestone or any of the cytogenetic milestones of the first year of TKI treatment demonstrate primary resistance. The loss of response after treatment milestones have been met, also known as relapse, describes secondary resistance. In either event, mutational analysis becomes a critical tool in guiding subsequent therapy. The consequences of not identifying patients with resistance are excessive in terms of patient outcomes and medical costs; the earlier the resistance is identified, the better chance a patient has of responding to the new therapy.[21] Together, these facts underscore the pivotal role of response monitoring in reducing patients' needless progression to the more advanced CML phases.

The success of TKI therapy also is dependent on patient adherence to prolonged oral therapy. Up to a third of patients routinely miss doses of their TKI medications and the clinical outcomes in these patients is poorer.[22] Patients who skipped >10 percent of their medications had a decreased six-year probability of a three-log qPCR reduction (28.4% vs. 94.5%; P<.001).[23] In a survey of CML patients, forgetfulness was the most common reason for non-adherence, followed by treatment-induced nausea, inconvenience, diarrhea, and muscle cramping. Financial concerns as a cause of non-adherence were self-reported by only 4 percent. Methods patients felt that might encourage adherence included improvements in side effect management, three-month prescriptions compared to monthly, better education, easier reporting of side effects, mail order prescription automatic refills, and reduced co-payments.[24] Since patients who lose response to therapy may require more expensive salvage TKI therapies to recapture response, or worse, may experience clinical disease progression resulting in expensive hospitalizations or transplantation, it is in the economic interest of MCOs to encourage member adherence to the oral TKI therapies.

Conclusion

Healthcare services for chronic disease states must be delivered in a timely and cost-conscience manner. It is the obligation of the MCO to coordinate member care plans that emphasize quality of life while still allocating resources responsibly. At an ever-escalating cost, targeted therapy has made a significant impact in the lives of patients afflicted with CML. In the case of treatment with TKIs, there are many tools available to support the organization's mission of maintaining financial integrity while providing patients with the most advanced treatment options. By 2030, the prevalence of CML is projected to more than double, and the costs of newly developed targeted cancer therapies are following a similar pattern. With a thorough understanding of the disease intricacies and judicious incorporation of best-practice guidelines, an expert care plan for members can ensure patient safety and fiscal responsibility.

MCO oversight in several critical aspects of CML treatment can help maximize clinical outcomes while minimizing economic burden. Although the clinical management

of the disease is the duty of the specialists, continued use or switching between expensive TKI therapies should be preceded by response-testing data. As previously noted, less than a quarter of CML patients are currently undergoing molecular monitoring according to published guidelines, at a risk of disease progression and increased costs. Evidence of disease control on a TKI corresponds to a high therapeutic value for the MCO because halting disease progression prevents the need for crisis interventions, such as repeat hospitalizations or stem cell transplants, which considerably escalate costs. First-line TKI therapies should be continued in patients who are meeting response milestones; however, upon treatment failure, it is in the best interest of all parties to allow the use of a new pharmacological agent that best harmonizes with a patient's baseline comorbidites or, when applicable, the mutational status of the disease. Additionally, since patient adherence to oral TKI therapy may be suboptimal, and may be associated with poorer outcomes, MCO efforts to improve adherence, such as physician notifications, may be cost-effective.

Although there have not been any head-to-head trials comparing the newer TKIs, their unique dosing, side-effect profiles, and mutational sensitivities can aid in optimizing the front-line therapy choice or be of use when the first-generation TKI has failed. For example, it may be prudent for the third-party payor to consider the patient's desire for a particular dosing schedule offered by one drug over another, given the cost and danger associated with poor patient compliance. In the event of primary or secondary response failure not due to adherence, it is imperative to obtain a mutational analysis in order to expose the underlying BCR-ABL dependent cause of treatment failure. Each of the most common BCR-ABL mutants will have at least one therapeutic agent that confers a sensitivity versus the other TKI options. Waiting to switch the TKI or switching with no regard to a possible mutational change results in poorer patient outcomes; therefore, the TKI response monitoring should be done in a timely manner as dictated by the NCCN guidelines in order to identify treatment failure as early as possible. Furthermore, when response milestones are not met, mutational analysis before the switch can facilitate the use of an optimal agent. This is critical because data indicates the patients who have failed TKI therapy are less likely to have good outcomes for the subsequent therapies. Reductions in clinical burden and economic waste can be significant through ensuring compliance with the response-monitoring guidelines. Given projected changes in the oncology field, with increasing use of effective but expensive therapies, the lessons learned from CML may guide broader medical care decisions in the MCO environment.

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The Future of Oral Oncology: Aligning Benefit Designs to Improve Quality and Contain Cost

Ira Klein, MD, National Medical Director, Clinical Thought Leadership, Office of the Chief Medical Officer, Aetna

Ira Klein, MD

The overall incidence of cancer in the United States is projected to increase by 45 percent in the next two decades, and direct medical costs associated with cancer are projected to increase exponentially as a result of both cost and quantity of cancer therapies.[1] With the number of new chemotherapy and oral cancer agents on the rise, U.S. payors have increased efforts to manage and control costs.[1,2] According to a 2008 report from the National Comprehensive Cancer Network (NCCN) Task Force, about one-quarter of the 400 antineoplastic agents currently in development are oral agents.[3] While the emergence of new oral cancer agents further expands the pool of available therapies, it also creates a challenge for payors and providers to restructure the design of traditional benefit plans.

Historically, benefit designs for coverage of intravenous (IV) and oral medications have determined that costs for IV medications be paid through the medical benefit, and costs for oral medications be paid through the pharmacy benefit; traditionally, oncology medications have been administered IV in a physician's office, infusion center, or hospital.[4,5] However, with the introduction of high-cost oral agents now being paid under the pharmacy benefit, we find situations where patients receiving oral agents encounter costs significantly higher than a patient would be expected to bear for receiving an IV agent.[5] Patient cost-sharing, on average, is higher for prescription benefits and lower for medical benefits; the implications of cost-sharing design greatly impact patients' out-of-pocket expenses.[4] The real issue here is medical and pharmacy benefit parity. There is a clear need for a collaboration of benefits and a structural change to benefit designs not only to assist patients, but also to gear up for the future of oncology with the sudden rise of oral chemotherapy agents.

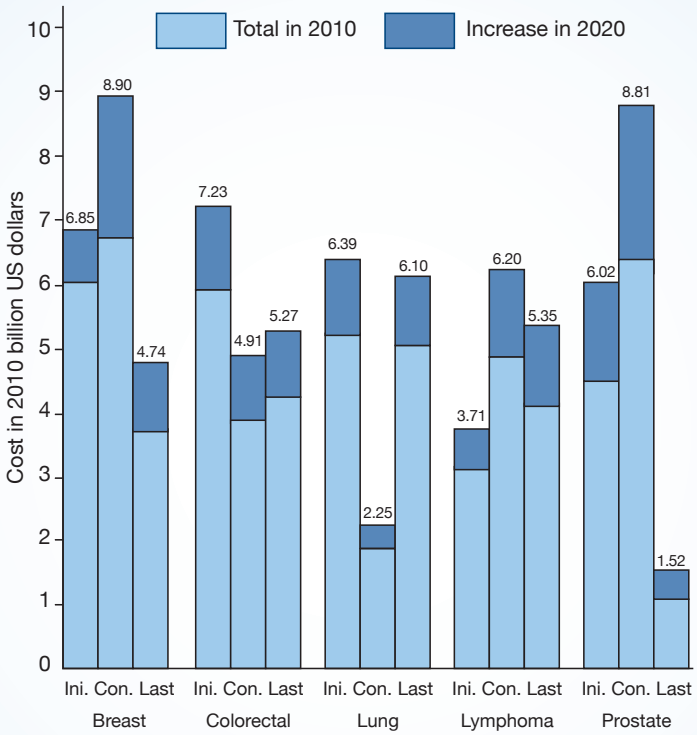
Currently, there are several state legislatures that have passed or are considering passing a "coverage parity" legislation that would require health plans to cover oral chemotherapy drugs with the same cost-sharing as IV chemotherapy drugs.[4] While states have started making changes, federal policy changes will also significantly impact patients, and providers considering Medicare patients constitute about 50 percent of

all cancer patients.[6] According to a study conducted in 2006, spending on oral chemotherapy drugs as a proportion of total pharmacy benefit costs has more than doubled from 0.3 percent in 2002 to 0.7 percent in 2006. Furthermore, with the incidence of cancer and our population of cancer survivors growing, costs are expected to increase with the development of new targeted therapies and patients requiring more courses of treatment (Figure 1).[7,8] Health plans are responding to this rise by increasing cost-sharing for members through different benefit designs.[4] These designs can limit clinical decision making for physicians and also lower adherence for patients since they may not be able to afford their medications. Therefore, by lowering cost shares and redesigning benefit structure, drug utilization and access can increase and potentially create better outcomes for patients.

Aside from financial issues, oral chemotherapy agents offer patients an array of features that were not previously available with IV chemotherapy. Oral oncology agents allow patients the convenience of taking them at home and reduces the amount of time spent at doctor's offices or hospitals for infusions. These medications are also associated with a lower cost of administration (direct costs in medical professional time, medical supplies, and IV pumps), and indirect costs related to missed work, travel time, and caregiver time.[7] Although oral agents may have fewer side effects and complications leading to improved tolerance, decreased adherence is a likely scenario due to decreased direct medical supervision.[5,7] Along with non-compliance, patients on chemotherapy frequently require dose adjustments and medication switches due to intolerability or development of mutations. Some pitfalls of oral therapy have been addressed by organizations through utilization of an oral chemotherapy cycle management program (CMP); cycle management programs were established to help manage patients and address potential adverse effects from using oral chemotherapy agents.[9] To minimize possible medication waste, pharmacies are instructed to dispense a partial month supply, followed by the balance, if the patient demonstrates adherence and tolerability. Partial fills could potentially create better patient outcomes and cost-savings through improving medication compliance, reducing hospitalizations, improving patient education, and monitoring of adverse effects.[9] While oral therapy offers some advantages, these regimens are quite complex and may have higher associated costs that decrease proper utilization. Accounting for these factors, oral therapy may not be for every patient but does offer a look into how far chemotherapy has come in recent years.

With cancer costs rapidly rising, payors are looking for ways to improve quality, reduce fragmentation, justify treatment variation, and decrease costs. Recently, there have been discussions on the use and implementation of pathways, including how much flexibility they allow providers, their effect on reimbursement and insurance, what data is used to design protocols, and what impact pathways will have on patient outcomes.[10] Pathways are integrated management plans that display goals for

Figure 1: Cancer Care Estimates in the U.S.[8]



Estimates of the national expenditures of cancer care in 2010 and the estimated increase in cost in 2020 due to the aging and growth of the U.S. population. Costs are shown by phase of care: initial year of diagnosis (Ini.), continuing care (Con.), and last year of life (Last).

Table 2

Potential Benefits and Limitations to Pathways[10-12]

Benefits	Limitations
Most up-to-date evidence-based medicine	Defined number of lines of therapy
Improved communication among healthcare professionals	Limited number of treatment options within each line
Improved CQI	Limited use of an agent to a single line
Improved patient outcomes/safety	Delayed inclusion of drug; drug shortages
Cost-effective care	Lack of individualization/personalized care
Decreased inappropriate variations in care	Pathways formulated to push specific drugs

patients and physicians, and provide appropriate sequencing and timing of actions necessary to achieve such goals with optimal efficiency using evidence-based medicine.[11] The introduction of clinical pathways could be an effective strategy for healthcare organizations to reduce or at least to control their processes and clinical performance variations.[13] These guidelines are a way to assist healthcare providers in clinical decision making and to improve care for patients through decreasing inappropriate variations in care, and by decreasing the use of less-effective therapies. This also allows oncologists to gain more refinement and knowledge of preferred treatments.[2,10] While pathways will provide recommendations for treating most patients, individual patient-specific factors also must be considered when applying these recommendations to be able to appropriately treat patients who fall outside the pathway.[10] Despite only 15 percent of oncology patients being treated according to pathways in 2010, this number could expand to 25 percent over the next few years as more health plans and providers institute pathway programs.[2]

For pathways to be effective and function properly, collaboration between payors and providers is crucial. Physicians directly and indirectly control the majority of medical care costs, and payors can dictate physician-prescribing patterns and behavior through reimbursement rates and financial incentives.[1] Without accountability or incentives, physicians might comply partially

Figure 2: Pathway Impact on Treatment Variation

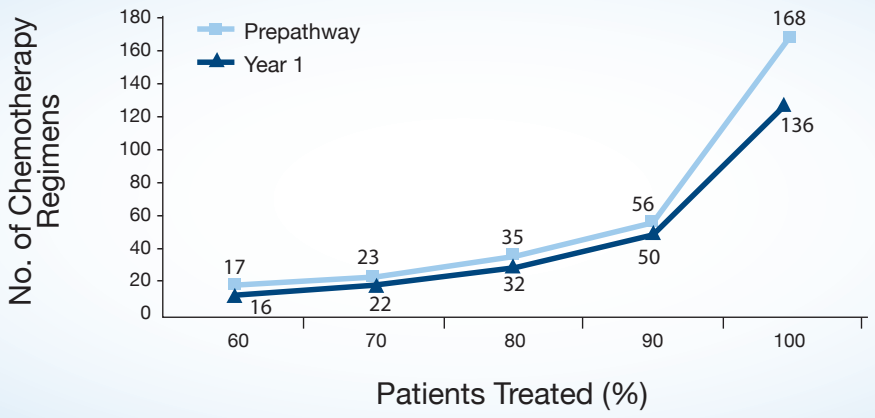
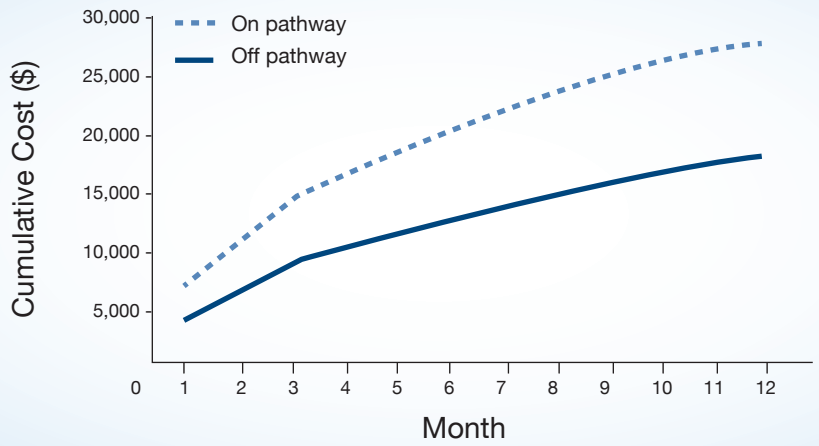


Figure 3: Impact of Pathway on Outpatient Costs



with the terms of a pathway or not participate at all so payors provide incentives to physicians who participate and meet compliance benchmarks.[1,10] Currently, many vendors and payors who employ pathways use the 80/20 rule: Providers should adhere to the pathway at least 80 percent of the time and are allowed to go off pathway 20 percent. This allows providers to have enough flexibility to personalize and tailor care to those individuals who would fall out of the pathway. A minimum compliance requirement also allows programs to track adherence and modifications to pathways, allowing them to better identify changes and patterns in therapy.[12]

A significant paradigm change in stakeholder collaboration between payor and provider will be necessary to implement a successful pathway; one such collaboration has been demonstrated by Blue Cross Blue Shield of Michigan (BCBSM).[1] The collaboration illustrated that an incentive-based program can achieve high levels of provider participation and compliance in pathways that lead to physician behavioral changes.[1] The results of BCBSM's pathway program showed that participating physician behavior changed significantly. Some observed behavioral changes included:

- A reduction in treatment variations (Figure 2)[1]
- Higher conversion rates of brand to generic when equally effective and equitoxic
- Use of molecular diagnostics to appropriately guide therapy
- Appropriate use of supportive care
- Decreased lines of therapy when evidence is lacking

As a result, these providers had lower rates of emergency room and hospital use.[1] While compliance monitoring was a challenge and at times incomplete due to a number of issues, this collaboration model can help with the development and implementation of future pathway designs.

While pathways appear to be the future of oncology, several issues need to be addressed to ensure their progress. The ability of a practice to integrate pathways into its software may be an issue, as the pathway software must be compatible with the pre-existing electronic health records.[2] Administration of pathways could be further complicated in cases where practices are contracted with multiple managed care organizations and their requirements for the use of pathways are different.[10] One solution to this barrier may be physician-developed pathways. Physician-designed pathways may also be preferable because provider uptake and compliance would be higher if they were given a role in the development process.[10] While data collection is crucial for pathway monitoring and effectiveness, it is proving to be quite difficult. Key data points that are essential for a pathway include: cancer staging, line of therapy, tumor characteristics, performance status, and the reason for any treatment alterations.[12] Most of this data does not make it into claims processing; these gaps

in information can make it difficult for health plans and physicians to have enough information at hand for determining the most appropriate treatment.[6] This is one challenge that pathways will need to address to continually improve and better reflect diagnostic information. And while clinical pathways will benefit both payors and providers, they could cause problems for drug manufacturers. If a drug is not placed in a pathway, the utilization and uptake of the drug may be slower and reimbursement could be difficult.[10] Companies will need to develop innovative drugs that can satisfy unmet goals to be included in pathways.[10]

In response to concerns about the cost-effectiveness of pathways, Highmark Blue Cross Blue Shield and CareFirst Blue Cross Blue Shield, through the University of Pittsburgh Medical Center, achieved savings of more than $1 million in only six months by controlling and reducing the use of Avastin® (bevacizumab) through clinical pathways in a study conducted in 2005.[12] Additionally, a 2010 report by Neubauer in *Journal of Oncology Practice* demonstrated significant cost-savings for patients with non-small cell lung cancer treated on pathway compared to patients treated off pathway with no difference in overall survival.[14] Overall, outpatient costs were 35 percent lower for patients treated on pathway, with an average 12-month cost of $18,042 for on-pathway versus $27,737 for off-pathway treatment (Figure 3).[14] Significant cost-savings were seen in both the first-line and the adjuvant treatment groups.[14]

Pathways are currently being designed primarily for chronic diseases and cancers, such as lung, breast, colorectal, and prostate, that are very expensive to treat and have several treatment options. Prostate cancer, in particular, is costing the U.S. economy roughly $10 billion annually, and although mortality rates are declining, costs are expected to rise due to aging demographics, early detection, and increased survival.[15] Furthermore, improved survival is now leading to an increased prevalence of biochemical recurrence and metastatic-castrate resistant prostate cancer (mCRPC).[15,16] While our population continues to age and chronic disease management becomes more and more prominent, collaboration between payor and provider is becoming more necessary. With the approval of new, expensive medications, it is more important than ever that health plans work with physicians to continually access guidelines and adjust pathways to control costs and maximize the value of each treatment option.

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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

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

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]

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.

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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.

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.

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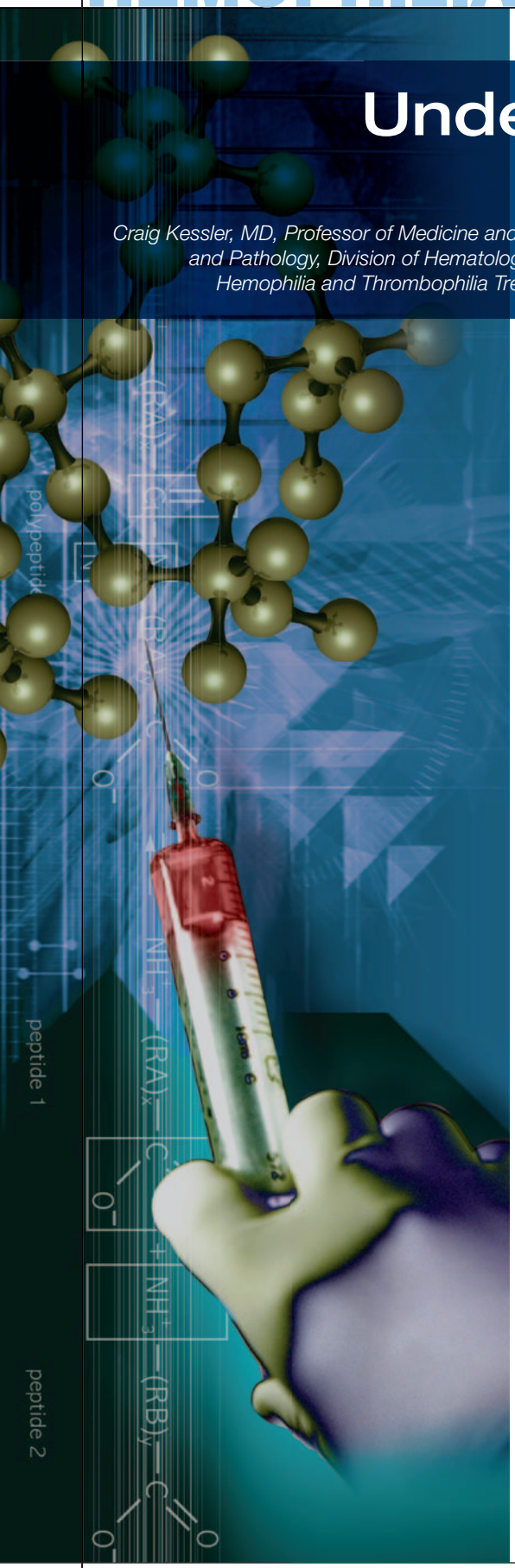

Understanding Hemophilia:
A Managed Care Review

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Hemophilia is an inherited bleeding disorder characterized by a defect in hemostasis that affects about 20,000 patients in the United States alone; the inability of the blood to properly coagulate is caused by a deficiency in either clotting factor VIII or clotting factor IX.[1] The deficient clotting factor delineates hemophilia into two forms: type A (factor VIII) and type B (factor IX). Hemophilia A accounts for about 80 percent of all hemophilia cases, with hemophilia B representing the other 20 percent; despite two different forms, clinical signs and symptoms are analogous.[2] Hemophilia is generally associated with spontaneous, heavy, and prolonged bleeding, often without obvious reason. The disorder is classified into three categories based on the clotting factor activity present in the blood: severe (<1 percent), moderate (1-5 percent), mild (>5 percent to <40 percent).[3]

Hemophilia can lead to serious internal bleeding complications and result in hospitalizations. One of the hallmark manifestations of hemophilia is bleeding into the joints called hemarthroses; if left untreated, it can lead to pain, swelling, and chronic and irreversible joint damage referred to as arthropathy. Hemophilic arthropathy is the result of recurrent joint bleeds and leads to joint immobility, reduction of daily activities, and reduced productivity.[4] Medical management of hemophilia emphasizes preventing degenerative joint disease, reducing bleeding complications, and improving quality of life.[5]

The cornerstone of disease management includes the use of replacement factor concentrates; these clotting-factor concentrates are quite expensive, and make up the bulk of treatment costs. Though dosing patterns vary, a typical patient receiving primary prophylaxis would require 2,000 IU of clotting factor three times per week; the average dose of factor VIII concentrate costs between $1,000 and $2,000 per dose.[6] This totals approximately $12,000 to $24,000 per month for concentrate costs alone, or $144,000 to $288,000 per year. According to a study conducted in 2008, the average annual healthcare expenditures for a patient with hemophilia covered by employer-sponsored insurance was about $155,000; clotting-factor concentrates represented approximately 75 percent of the total expense.[7]

In the same year, the annual average Medicaid expenditure for patients with hemophilia was estimated at about $143,000.[8] While treatment varies based on type of concentrate administered and disease severity, it is easy to see the financial burden hemophilia can put on patients and health plans.

General Treatment Approach

While the mainstay of treatment is the management of hemostasis with the use of factor replacement concentrates, these patients require comprehensive management, including treatment of bleeding episodes, treatment for patients with inhibitors, and the treatment of other complications, such as joint and liver disease. The level of severity is generally used to determine which treatment modality is most appropriate. There are three main patient populations: type A, type B, and patients with inhibitors. Each of these populations require a different treatment approach.

For those with mild to moderate hemophilia, the standard treatment of choice is desmopressin (DDVAP).[6] Desmopressin, a synthetic form of vasopressin, helps stimulate the release of stored factor VIII; however, the more this product is used, the less effective it becomes. Taking this into consideration along with mild disease severity, DDVAP is given only in limited situations.[9] Some observed benefits with DDVAP use include no risk of blood-borne disease, lower costs relative to factor concentrates, avoided use of factor concentrates, and sufficient bleeding control for mild bleeding episodes. The average cost for a dose of desmopressin (21 μg) is about $100 in the United States.[6]

Though DDVAP provides sufficient hemostasis in some patients, it is not effective for the treatment of severe hemophilia; factor concentrates are required for these patients. There are currently two different types of factor concentrates available: either plasma-based or recombinant. Plasma-based concentrates are more cost-effective than recombinant-factor concentrates, but they do carry a higher risk for blood-borne diseases, such as hepatitis B, hepatitis C, and HIV.[9] New recombinant-factor concentrates are also being formulated with longer half-lives. The emergence of longer-acting agents can allow for less frequent dosing to attain desired plasma levels and could also potentially lead to an increase in medication adherence with better control of bleeding episodes. For hemophilia A, patients will receive factor VIII concentrates, while hemophilia B patients require factor IX concentrates. Doses of factor concentrate are calculated based on severity and location of the bleed with the goal to maintain a desired factor level (Table 1, page 35).[10] These guidelines are used to help steer clinical decision making, but there is still much debate on whether to use on-demand therapy or prophylactic therapy.

On-Demand vs. Prophylaxis

With healthcare costs on the rise, physicians and health plans are searching for ways to reduce costs while keeping patient care a top priority. The clinical management of hemophilia is currently shifting from on-demand treatment with clotting-factor concentrates to prophylaxis therapy. The idea is that if we prevent bleeds from happening in the first place, instead of treating bleeds as they occur, we can reduce the incidence of hemophilic arthropathy and other long-term complications that can further increase medical expenditures. Prophylactic therapy is well accepted for the pediatric population, usually beginning at an early age to prevent joint and other damage from developing. According to one study conducted in 2011, children who received prophylactic therapy compared to on-demand therapy had significantly fewer hemarthroses ($p<0.02$); this study also showed that prophylaxis was more effective when started earlier (<36 months).[11] That same study demonstrated that the cost of prophylaxis in the pediatric population was about 2.4 to 3.1 times greater than the

Average Expenditures

According to a study conducted in 2008, the average annual healthcare expenditures for a patient with hemophilia covered by employer-sponsored insurance was about $155,000; clotting-factor concentrates represented approximately 75 percent of the total expense.[7]

cost of on-demand therapy. However, prophylaxis therapy significantly reduced the number of joint bleeds and improved the quality of life for patients.[11]

While primary prophylaxis has been established to be extremely beneficial when started at a young age prior to the onset of joint bleeding, there is less evidence-based information on the value of secondary prophylaxis in adults with mild or moderate hemophilia. A study conducted in 2010 looked at the benefit of secondary prophylaxis versus on-demand therapy in adults with prior joint bleeds over two six-month periods using the same factor VIII concentrate. The study showed that patients who received prophylactic therapy had significantly fewer episodes of hemarthroses, reduced disability, and improved quality of life.[12] Additionally, the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation recommends prophylactic therapy for most patients and finds it should be instituted prior to the onset of frequent bleeding to provide the most benefit.[13] Current clinical practice suggests that patients who experience more than two to three bleeding episodes per year should be on prophylaxis to avoid permanent, irreversible joint damage.

The ongoing SPINNART trial should provide more specific guidance and help design better treatment algorithms for prophylaxis therapy. While prophylaxis therapy is proven to improve patient outcomes and quality of life, it remains underused primarily due to cost issues. To address this, regimens are being tailored to patients' specific needs to reduce costs and waste by dispensing the most appropriate vial size. Additional studies need to be conducted to establish criteria regarding when to start prophylactic treatment, the optimum regimen to apply, and when to discontinue this management strategy, if at all.[3] Furthermore, while there are studies available that show the effectiveness prophylaxis therapy has on improving quality of life and reducing joint complications, studies need to be conducted to determine the long-term cost-effectiveness of prophylaxis versus on-demand therapy.

Management of Inhibitors

One of the most significant limitations of clotting factor replacement therapy is the development of neutralizing antibodies, known as inhibitors. Inhibitors essentially render the replacement factor concentrate inactive or greatly reduce its effectiveness, resulting in decreased disease management for patients. Inhibitors develop in approximately 30 percent of patients with severe hemophilia A and up to 5 percent of those with hemophilia B. This places these patients at increased risk for serious bleeding episodes, extensive joint damage, and other complications.[11] While studies have identified some risk factors for the development of inhibitors, the jury is still out on the exact cause. Risk factors include age, race, type of hemophilia, presence of immune disorders, frequency, and the dose of treatment.[1] Inhibitors typically occur with increased use of factor concentrate (within the first 50 times of use); the implications this has on prophylaxis therapy has yet to be determined, but it is suggested that low-dose prophylaxis therapy could reduce the incidence of inhibitor formation.[1,12]

The healthcare costs associated with this patient subset is staggering due to the cost and amount of treatment required. The treatment for patients with inhibitors requires larger doses of clotting factor or the use of bypassing agents, such as recombinant activated factor VIIa (Factor VII; NovoSeven®) or plasma-derived activated prothrombin complex concentrate (APCC; FEIBA), to control bleeding. According to a study conducted in 2008, the average yearly healthcare expenditures for patients with hemophilia and inhibitors covered by employer-sponsored insurance was about five times higher than for patients without inhibitors ($155,000 vs. $697,000).[7] In the same year, the average annual Medicaid expenditure for patients with hemophilia and inhibitors was about 3.6 times higher than individuals without inhibitors.[8]

It has been known for several years that on-demand use of bypassing agents effectively controls about 80 percent of bleeding episodes in this difficult-to-manage population.[14] The 2011 Prophylaxis with Factor Eight Inhibitor Bypassing Activity (Pro-FEIBA) study, conducted among patients at 16 hemophilia treatment centers (HTCs) in Europe and the United States, provided evidence that prophylactic APCC three times weekly was clinically superior to on-demand therapy for these patients, providing a 62 percent reduction in all bleeding and a 61 percent reduction in joint bleeds.[14] This data is particularly encouraging considering the study was designed as secondary prophylaxis, defined as prophylaxis instituted after the onset of joint bleeding—a situation where suppressing bleeds is usually much more difficult. In the Pro-FEIBA study, the cost of prophylactic treatment

Table 1

Hemophilia Hemorrhage Sites and Types of Therapy

Site of Hemorrhage	Desired Hemostatic Factor Level (% of normal)	Comments
Joint	50%-70%	Rest/immobilization/physical therapy rehabilitation following bleed; several doses may be necessary to prevent or treat target joint
Muscle	30%-50% for most sites	
	70%-100% for thigh, iliopsoas, or nerve compression	Risk of significant blood loss with femoral/retroperitoneal bleed; bed rest for iliopsoas or other retroperitoneal bleeding
Oral mucosa	30%-50%	May try antifibrinolytic or topical thrombin prior to factor replacement for minor bleeding; higher factor levels may be needed for tongue swelling or risk of airway compromise; antifibrinolytic therapy should be used following factor replacement; do not use with aPCCs or PCCs
Gastrointestinal	Initially 100%, then 30% until healing occurs	Endoscopy is highly recommended; antifibrinolytic therapy may be useful
Hematuria	30% if no trauma	
	70%-100% if traumatic	If no pain or trauma, consider bed rest and fluids for 24 hours; factor should be given if hematuria persists; evaluate if hematuria persists; if trauma to abdomen or back, perform imaging and give aggressive factor replacement
Central nervous system	Initially 100%, then 50%-100% for 10-14 days	Lumbar puncture requires prophylactic factor coverage
Trauma or surgery	Initially 100%, then 50% until wound healing complete	Perioperative and postoperative management plan must be in place preoperatively; evaluation for inhibitors is crucial prior to elective surgery

Treatment Type	Advantages	Disadvantages
Plasma-derived products	Generally effective Cost-effective Widely available	Reinjection necessary Risk of pathogen transfer (despite some cleansing methods) Formation of inhibitors (in some patients)
Recombinant factors	Generally effective Safer than plasma-derived products	Longer recovery time than plasma-derived products More expensive than plasma-based products Difficult to manufacture Formation of inhibitors (in some patients)
Gene therapy	Theoretically promising therapy	Mutagenesis of inserted gene Surgical procedure may be necessary Limited use in human subjects Expensive Formation of inhibitors (in some patients)
aPCC for patients with inhibitors	Generally effective (not as effective as recombinant factors) No immune response	Possible resistance to treatment Risk of cardiovascular problems Theoretical risk of pathogenic infection Risk of liver damage Expensive due to reinjections
Recombinant FVIIa for patients with inhibitors	Generally effective No immune response Reduced need to reinject product More cost-effective than aPCC	Possible resistance to treatment Cardiovascular problems Other side effects
Immune therapy for patients with inhibitors	Generally effective (when used in combination with clotting factor replacement) No immune response	Infusions accompanied by side effects Strenuous treatment Possible increased susceptibility to pathogens Patient monitoring necessary Expensive

Table 2 Hemophilia Pipeline

Manufacturer	Hemophilia A/B	Drug	Treatment / Prophylaxis	Phase I	Phase II	Phase III	Filed	Phase IV
Biogen	A	rFVIIIFc	Treatment				X	
	B	rFIXFc	Treatment			X		
Novo	A	Turoctocog alfa (NN7008)	Treatment / Prophylaxis				X	
	A	N8-GP (NN7088)	Treatment / Prophylaxis			X		
	B	N9-GP (NN7999)	Treatment / Prophylaxis			X		
	A/B	mAb2021 (NN7415)	Prophylaxis	X				
Baxter	A	Advate antihemophilic factor	Prophylaxis					X
	B	Rixubis (BAX 326)	Treatment					X
	A	BAX 855 (PEGylated recombinant factor VIII)	Treatment / Prophylaxis			X		
Bayer	A	BAY 86-6150	Treatment			X		
	A	BAY 94-9027	Treatment / Prophylaxis			X		
Octopharma	A	Human-cl rhFVIII	Treatment / Prophylaxis			X		
CSL Behring	B	CSL 654 rIX-FP	Treatment / Prophylaxis			X		
	A	CSL 627 rFVIII	Treatment		X			
	A	CSL 689 rVIIa-FP	Treatment / Prophylaxis	X				
Cangene	B	IB1001	Treatment / Prophylaxis				X	

was 2.4 times greater than that of on-demand therapy ($493,633 vs. $205,549, per patient, based on an average cost of $1.56 per unit of APCC for patients in the United States).[14] Despite this cost, the National Hemophilia Foundation recommends that bypassing agents be used to manage patients with inhibitors as a prophylactic strategy to control and prevent bleeds.[13] It should be noted that studies of prophylactic bypassing agents still report some episodes of early death compared to patients without inhibitors. More studies need to be conducted to establish a more effective management strategy for these patients.

An alternative strategy for managing these patients is to perform immune tolerance induction (ITI) when the inhibitor is first detected. These patients receive frequent high doses of factor concentrate over a period of months to a few years in an effort to desensitize the immune system and prevent it from responding with inhibitor formation.[15] When this strategy is successful, inhibitors are eliminated, returning the patient to a normal response to factor concentrates. Limiting this practice are the exorbitant costs of this approach and potential side effects, such as risk for thrombosis. The best ITI dosing schedule has yet to be defined, though the ongoing Immune Tolerance Induction Study is comparing the effectiveness and safety of different dosing regimens in patients with severe hemophilia A.

Hepatitis and Liver Disease

Despite the availability of recombinant concentrates, improved blood donor screening protocols, and viral inactivation methods, chronic hepatitis and liver disease remains a major health concern in the management of adult hemophilia patients. Chronic hepatitis C (HCV) infection can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) and represents the leading cause of death in adult patients with hemophilia.[16] These patients also cost health plans more to manage; according to a study conducted in 2008, the average cost of treating hepatitis-infected adults with hemophilia was 1.5 times greater than for those without an infection.[7]

The use of factor concentrates should become more cost-effective and the utilization of prophylaxis therapy should increase with the evolution of pharmacokinetic-based dosing. This strategy allows physicians to appropriately dose patients and offers the potential for cost-savings in those patients who reach hemostasis from lower-than-average doses.

Standard treatment of HCV has commonly involved pegylated interferon-based regimens in combination with ribavirin. This therapy achieved sustained virologic response rates of about 40 percent in patients with this HCV subtype.[16] In 2011, two HCV-specific, direct-acting protease inhibitors—telaprevir (Incivek®) and boceprevir (Victrelis®)—received FDA approval for the treatment of genotype 1 HCV, the most common type of HCV in the United States.[17] Studies have shown that when used in combination with pegylated interferon and ribavirin, triple therapy with either telaprevir or boceprevir significantly improves sustained virologic response rates to around 70 percent in previously untreated patients and 65 percent in previously treated patients with genotype 1a HCV.[16] Although these drugs provide outstanding virologic response not previously observed, they could add up to $50,000 to the cost of treating HCV.[16] They may be worth the price if they can decrease the duration of required therapy, lower viral resistance, and prevent liver failure and the need for transplantation.

Patients with HCV are at an increased risk of developing HCC; the projected costs of HCV-related disease are expected to exceed $10 billion between 2010 and 2019.[18] According to a 2012 report, triple therapy can reduce the lifetime risk for HCC by 38 percent and 28 percent, respectively, compared with standard therapy for patients with mild and advanced fibrosis.[19] The addition of boceprevir or telaprevir represents an additional medication cost of $1,100 and $4,100 per week, respectively.[19] However, to avoid the development of more serious sequelae, including the need for a transplant or chemotherapy in the event of HCC transformation, triple therapy can be a cost-effective strategy.[19]

Earlier generations of protease inhibitors developed for HIV have been associated with an increased risk of bleeding complications, but it is not yet known whether HCV-specific protease inhibitors carry a similar risk. Both boceprevir and telaprevir are associated with worsening of anemia; approximately 40 percent of patients receiving telaprevir and about 50 percent receiving boceprevir in clinical trials developed anemia, compared to close to 20 percent developing anemia with PEG/ribavirin alone.[16] While increased bleeding does not appear to be a major adverse event with the new protease inhibitors, the development of anemia may be an indicator that some bleeding is occurring. Despite the efficacy these agents have displayed, further studies need to be conducted in patients with hemophilia to uncover any increased risk of bleeding.

Hemophilia Treatment Centers and 340B Drug Pricing

Due to the complexity and costly nature of hemophilia management, health plans and legislatures have been improving care throughout the years with the establishment of HTCs and a unique drug-pricing program. In the nearly 50 years since the first HTC network was established, approximately 140 federally funded centers are offering comprehensive medical care and preventive services to more than 15,000 patients with hemophilia in the United States.[15,20] HTCs have made a significant impact on improving the morbidity and mortality associated with hemophilia and its complications. According to a study conducted in 2000, HTCs were able to reduce the risk for mortality due to hemophilia-related complications by about 40 percent compared to those who did not receive care at a treatment center.[21]

Since HTCs are able to follow patients more comprehensively, cost-savings can be achieved through fine-tuning dosing strategies through pharmacokinetic studies. The use of pharmacokinetic testing, with computer-simulated doses and intervals, has been used to achieve optimal predetermined trough activity levels of factor concentrate.[3] The use of factor concentrates should become more cost-effective and the utilization of prophylaxis therapy should increase with the evolution of pharmacokinetic-based dosing. This strategy allows physicians to appropriately dose patients and offers the potential for cost-savings in those patients who reach hemostasis from lower-than-average doses.

HTCs offer superior patient outcomes and do so at lower costs compared with home care providers. HTCs operate under the regulations of the federal 340B Drug Pricing Program, established in 1992, which provides access to reduced-price prescription drugs. HTCs have the ability to acquire hemophilia medications at a discounted price of the average wholesale price reduced by a minimum rebate percentage. HTCs, by law, can negotiate the prices with the manufacturers and eliminate the influence of home care companies that raise prices to provide patients with their medications at a significantly lower price.

Recent Developments

In previously untreated patients with severe hemophilia A, the impact that factor products and product switching have on clinically relevant inhibitor development has been largely unknown. However, a recent study published in the *New England Journal of Medicine* helps to provide an answer to this question. The study evaluated 574 children with severe hemophilia A and collected data on all clotting-factor administration. The primary outcome measure was inhibitor development. The authors concluded that recombinant and plasma-derived factor VIII products confer similar risks for inhibitor development and that switching among products was not associated with an increased risk of developing inhibitors.[22] This study may provide healthcare insurers with supporting evidence to pursue new management strategies promoting appropriate clinical care, while containing the escalating costs of treating patients with hemophilia.

Editorial assistance provided by Alice McCarthy

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For example, gestational diabetes and diabetes among pregnant women are both associated with increased risk of health complications for both the mother and infant.[1-6] A maternal diagnosis of gestational diabetes is associated with high rates of complicated births and intensive care utilization, as well as neonatal hypoglycemia, respiratory distress syndrome, and macrosomia (large body size) in newborns.[2,3] Pre-existing diabetes in pregnancy is further associated with preterm (early) birth and higher risk of miscarriage when blood sugar remains high.[4] To achieve the best possible outcomes in pregnancies complicated by diabetes, it is crucial to balance optimal glycemic control and safety for both the woman and the fetus.[1,5,6]

Children with diabetes are also at increased risk for costly disease-related complications like impaired growth and pubertal development, as well as other autoimmune diseases.[7] Inadequate diabetes care in childhood can lead to lower quality of life and earlier development of the complications of diabetes.[7] Similarly, among the elderly, diabetes is associated with lower levels of cognitive function and greater cognitive decline.[8]

That's why, at Novo Nordisk, we're looking for glycemic management solutions for your whole population.

References: 1. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013;36(suppl 1):S11-S66. **2.** Agency for Healthcare Research and Quality. Gestational diabetes: caring for women during and after pregnancy. August 2009. http://effectivehealthcare.ahrq.gov/ehc/products/107/163/2009_0804GDM_Clinician_final.pdf. Accessed May 20, 2013. **3.** Wier LM, Witt E, Burgess J, Elixhauser A. Hospitalizations related to diabetes in pregnancy, 2008. HCUP Statistical Brief #102. December 2010. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb102.pdf. Accessed June 11, 2013. **4.** Centers for Disease Control and Prevention. Diabetes & pregnancy. http://www.cdc.gov/features/diabetespregnancy/. Accessed May 20, 2013. **5.** International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676-682. **6.** Kitzmiller JL, Block JM, Brown FM, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care.* 2008;31(5):1060-1079. **7.** International Diabetes Federation. IDF/ISPAD global guideline for diabetes in childhood and adolescence. http://www.ispad.org/resource-type/idfispad-2011-global-guideline-diabetes-childhood-and-adolescence. Published 2011. Accessed May 20, 2013. **8.** Kirkman MS, Briscoe BJ, Clark N, et al. Diabetes in older adults. *Diabetes Care.* 2012;35(12):2650-2664.

changing diabetes®

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novo nordisk®

VICTRELIS® (boceprevir) plus
peginterferon alfa/ribavirin (PR) vs PR

AN ADDED EDGE AGAINST CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE 1 (G1)

MERCK

INDICATIONS AND USAGE

VICTRELIS is indicated for the treatment of chronic HCV G1 infection, in combination with PR, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including prior null responders, partial responders, and relapsers.

The following points should be considered when initiating VICTRELIS for treatment of chronic HCV infection:

- VICTRELIS must not be used as monotherapy and should only be used in combination with PR.
- The efficacy of VICTRELIS has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors.
- Poorly interferon responsive patients who were treated with VICTRELIS in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR.

Choose VICTRELIS triple therapy for chronic HCV G1 adult patients with compensated liver disease.

To learn more about VICTRELIS, visit victrelis.com.

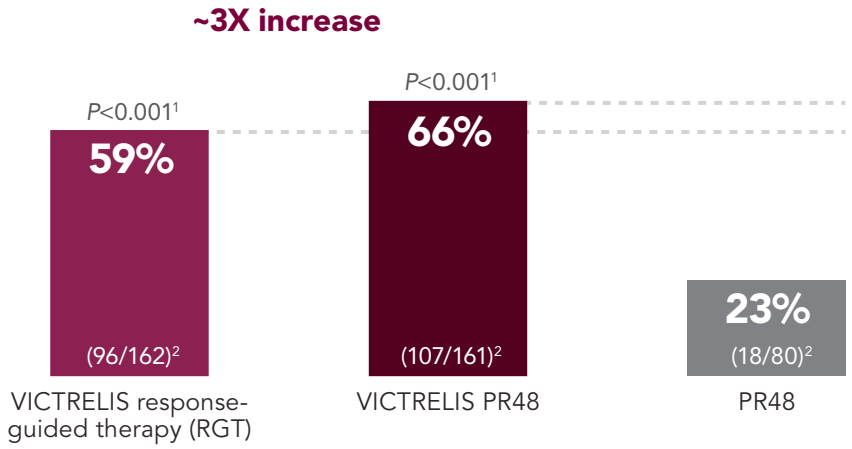
VICTRELIS® boceprevir 200 MG CAPSULES

VICTRELIS® (boceprevir) + PR vs PR: In adult patients with chronic HCV G1 infection with compensated liver disease who previously failed PR therapy

An added edge that nearly tripled virologic cure (SVR)[a] rates

59% to 66% overall SVR rates with VICTRELIS + PR vs 23% with PR for 48 weeks (PR48)

Overall SVR rates



- VICTRELIS, in combination with PR, has not been studied in patients documented to be historical null responders (<2-$\log_{10}$ HCV-RNA decline by Treatment Week 12) during prior therapy with PR.

SELECTED SAFETY INFORMATION

- All contraindications to PR also apply since VICTRELIS must be administered with PR.
- Because ribavirin may cause birth defects and fetal death, VICTRELIS in combination with PR is contraindicated in pregnant women and in men whose female partners are pregnant. Avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy; have monthly pregnancy tests; and use 2 or more forms of effective contraception during treatment and for at least 6 months after treatment has concluded. One of these forms of contraception can be a combined oral contraceptive product containing at least 1 mg of norethindrone. Oral contraceptives containing lower doses of norethindrone and other forms of hormonal contraception have not been studied or are contraindicated.
- VICTRELIS is contraindicated in patients with a history of a hypersensitivity reaction to VICTRELIS.
- VICTRELIS is contraindicated in coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. VICTRELIS is also contraindicated in coadministration with potent CYP3A4/5 inducers, where significantly reduced VICTRELIS plasma concentrations may be associated with reduced efficacy.
- Drugs that are contraindicated with VICTRELIS include: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort (hypericum perforatum), lovastatin, simvastatin, drospirenone, *Revatio®* (sildenafil) or *Adcirca®* (tadalafil) (when used for the treatment of pulmonary arterial hypertension), pimozide, triazolam, and orally administered midazolam.

RESPOND-2 Study Design

A randomized, parallel-group, double-blind, Phase 3 study in previously treated subjects with chronic HCV G1 infection (N=403). All subjects received a 4-week lead-in of PR (peginterferon alfa-2b 1.5 µg/kg/week subcutaneously plus weight-based ribavirin 600 to 1,400 mg/day orally in divided doses BID), followed by either a response-guided regimen that consisted of 32 weeks of triple therapy with PR + VICTRELIS 800 mg TID, followed by 12 additional weeks of PR if virus detected by Treatment Week 8 (VICTRELIS RGT); 44 weeks of triple therapy (VICTRELIS PR48); or 44 weeks of PR + placebo (PR48). Primary study end point was SVR (defined as plasma HCV-RNA <25 IU/mL at Follow-up Week 24). All subjects with detectable HCV-RNA in plasma at Treatment Week 12 were discontinued from treatment. Plasma HCV-RNA results at Follow-up Week 12 were used if plasma HCV-RNA results at Follow-up Week 24 were missing. Mean age of subjects randomized was 53 years. The racial distribution of subjects was 85% white, 12% black, and 3% others. The distribution by gender was 67% men and 33% women.[1]

BID = twice a day; RESPOND-2 = Retreatment with HCV Serine Protease Inhibitor Boceprevir and PR-2; RNA = ribonucleic acid; TID = 3 times a day.

[a]Sustained virologic response (SVR) was defined as plasma HCV-RNA <25 IU/mL at Follow-up Week 24. This is generally considered a "virologic cure," as the rate of late relapse (beyond 24 weeks) is <1%.[3,4]

SELECTED SAFETY INFORMATION *(cont.)*

- Anemia and/or Neutropenia – The addition of VICTRELIS to PR is associated with an additional decrease in hemoglobin concentrations compared with PR alone and/or may result in worsening of neutropenia associated with PR therapy alone. Dose reduction or discontinuation of peginterferon alfa and/or ribavirin may be required. If peginterferon alfa or ribavirin is permanently discontinued, VICTRELIS must also be discontinued. Dose reduction of VICTRELIS is not recommended. VICTRELIS must not be administered in the absence of PR.
- Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating combination therapy with VICTRELIS. Complete blood counts should be obtained at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.
- Serious acute hypersensitivity reactions (eg, urticaria, angioedema) have been observed during combination therapy with VICTELIS and PR. If such an acute reaction occurs, combination therapy should be discontinued and appropriate medical therapy immediately instituted.
- The most commonly reported adverse reactions (>35%) in clinical trials in adult patients receiving the combination of VICTRELIS with PR were: fatigue, anemia, nausea, headache, and dysgeusia. Of these commonly reported adverse reactions, fatigue, anemia, nausea, and dysgeusia occurred at rates ≥5% above the rates for PR alone in either clinical study. The incidence of these adverse reactions in previously untreated subjects that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (58% vs 59%), anemia (50% vs 30%), nausea (46% vs 42%), and dysgeusia (35% vs 16%), respectively. The incidence of these adverse reactions in previous treatment failure patients that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (55% vs %50%), anemia (45% vs 20%), nausea (43% vs 38%), and dysgeusia (44% vs 11%), respectively.
- VICTRELIS is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5. The potential for drug-drug interactions must be considered prior to and during therapy.

Please see Brief Summary of Prescribing Information on the pages that follow.

References: 1. Bacon BR, Gordon SC, Lawitz E, et al; for HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364(13):1207–1217. **2.** Birnkrant D. Direct-acting antivirals: a new era for the treatment of chronic hepatitis C. Slide deck presented at: Antiviral Drugs Advisory Committee Meeting; April 27–28, 2011; Silver Spring, MD. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254076.pdf. Accessed August 24, 2012. **3.** Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011;54(4):1433–1444. **4.** Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis.* 2011;52(7):889–900.

Choose VICTRELIS triple therapy for chronic HCV G1 adult patients with compensated liver disease.

To learn more about VICTRELIS, visit victrelis.com.

VICTRELIS® boceprevir

VICTRELIS® (boceprevir)

CONTRAINDICATIONS

Contraindications to peginterferon alfa and ribavirin also apply to VICTRELIS combination treatment.

VICTRELIS, in combination with peginterferon alfa and ribavirin, is contraindicated in:

- Pregnant women and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with ribavirin.
- Patients with a history of a hypersensitivity reaction to boceprevir.
- Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including those in Table 2.
- Coadministration with potent CYP3A4/5 inducers, where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy, including those in Table 2.

Table 2: Drugs that are contraindicated with VICTRELIS

Drug Class	Drugs Within Class that are Contraindicated With VICTRELIS	Clinical Comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Increased alfuzosin concentrations can result in hypotension.
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to VICTRELIS
Antimycobacterial Agents	Rifampin	May lead to loss of virologic response to VICTRELIS.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response to VICTRELIS.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.
Oral Contraceptives	Drospirenone	Potential for hyperkalemia.
PDE5 enzyme Inhibitor	REVATIO® (sildenafil) or ADCIRCA® (tadalafil) when used for the treatment of pulmonary arterial hypertension*	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam†	Prolonged or increased sedation or respiratory depression.

* See *Drug Interactions, Table 5* for coadministration of sildenafil and tadalafil when dosed for erectile dysfunction.
† See *Drug Interactions, Table 5* for parenterally administered midazolam.

WARNINGS AND PRECAUTIONS

Pregnancy (Use with Ribavirin and Peginterferon Alfa)

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. One of these forms of contraception can be a combined oral contraceptive product containing at least 1 mg of norethindrone. Oral contraceptives containing lower doses of norethindrone and other forms of hormonal contraception have not been studied or are contraindicated. Routine monthly pregnancy tests must be performed during this time.

Anemia (Use with Ribavirin and Peginterferon Alfa)

Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of VICTRELIS to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be obtained pretreatment, and at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. If hemoglobin is less than 10 g/dL, a decrease in dosage or interruption of ribavirin is recommended; and if hemoglobin is less than 8.5 g/dL, discontinuation of ribavirin is recommended. If ribavirin is permanently discontinued for management of anemia, then peginterferon alfa and VICTRELIS must also be discontinued.

Refer to the Package Insert for ribavirin for additional information regarding dosage reduction and/or interruption.

In clinical trials with VICTRELIS, the proportion of subjects who experienced hemoglobin values less than 10 g/dL and less than 8.5 g/dL was higher in subjects treated with the combination of VICTRELIS with PegIntron®/REBETOL® than in those treated with PegIntron/REBETOL alone (see Table 4). With the interventions used for anemia management in the clinical trials, the average additional decrease of hemoglobin was approximately 1 g/dL.

In clinical trials, the median time to onset of hemoglobin less than 10 g/dL from the initiation of therapy was similar among subjects treated with the combination of VICTRELIS and PegIntron/REBETOL (71 days with a range of 15–337 days), compared to those who received PegIntron/REBETOL (71 days with a range of 8–337 days). Certain adverse reactions consistent with symptoms of anemia, such as dyspnea, exertional dyspnea, dizziness and syncope were reported more frequently in subjects who received the combination of VICTRELIS with PegIntron/REBETOL than in those treated with PegIntron/REBETOL alone.

In clinical trials with VICTRELIS, dose modifications (generally of PegIntron/REBETOL) due to anemia occurred twice as often in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL (26%) compared to PegIntron/REBETOL (13%). The proportion of subjects who discontinued study drug due to anemia was 1% in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL and 1% in subjects who received PegIntron/REBETOL. The use of erythropoiesis stimulating agents (ESAs) was permitted for management of anemia, at the investigator's discretion, with or without ribavirin dose reduction in the Phase 2 and 3 clinical trials. The proportion of subjects who received an ESA was 43% in those treated with the combination of VICTRELIS with PegIntron/REBETOL compared to 24% in those treated with PegIntron/REBETOL alone. The proportion of subjects who received a transfusion for the management of anemia was 3% of subjects treated with the combination of VICTRELIS with PegIntron/REBETOL compared to less than 1% in subjects who received PegIntron/REBETOL alone.

Thromboembolic events have been associated with ESA use in other disease states; and have also been reported with peginterferon alfa use in hepatitis C patients. Thromboembolic events were reported in clinical trials with VICTRELIS among subjects receiving the combination of VICTRELIS with PegIntron/REBETOL, and among those receiving PegIntron/REBETOL alone, regardless of ESA use. No definite causality assessment or benefit risk assessment could be made for these events due to the presence of confounding factors and lack of randomization of ESA use.

A randomized, parallel-arm, open-label clinical trial was conducted in previously untreated CHC subjects with genotype 1 infection to compare use of an ESA versus ribavirin dose reduction for initial management of anemia during therapy with VICTRELIS in combination with peginterferon alfa-2b and ribavirin. Similar SVR rates were reported in subjects who were randomized to receive ribavirin dose reduction compared to subjects who were randomized to receive an ESA. In this trial, use of ESAs was associated with an increased risk of thromboembolic events including pulmonary embolism, acute myocardial infarction, cerebrovascular accident, and deep vein thrombosis compared to ribavirin dose reduction alone. The treatment discontinuation rate due to anemia was similar in subjects randomized to receive ribavirin dose reduction compared to subjects randomized to receive an ESA (2% in each group). The transfusion rate was 4% in subjects randomized to receive ribavirin dose reduction and 2% in subjects randomized to receive an ESA.

Ribavirin dose reduction is recommended for the initial management of anemia.

Neutropenia (Use with Ribavirin and Peginterferon Alfa)

In Phase 2 and 3 clinical trials, seven percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had neutrophil counts of less than 0.5 x 10^9/L compared to 4% of subjects receiving PegIntron/REBETOL alone (see Table 4). Three subjects experienced severe or life-threatening infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving the combination of VICTRELIS® (boceprevir) with PegIntron/REBETOL. Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating VICTRELIS/peginterferon alfa/ribavirin combination therapy. Complete blood counts should be obtained at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. Decreases in neutrophil counts may require dose reduction or discontinuation of peginterferon alfa and ribavirin. If peginterferon alfa and ribavirin are permanently discontinued, then VICTRELIS must also be discontinued.

Refer to Package Inserts for peginterferon alfa and ribavirin for additional information regarding dose reduction or discontinuation for peginterferon alfa and ribavirin.

Hypersensitivity

Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with VICTRELIS, peginterferon alfa and ribavirin. If such an acute reaction occurs, combination therpay should be discontinued and appropriate medical therapy immediately instituted.

Drug Interactions

See Table 2 for a listing of drugs that are contraindicated for use with VICTRELIS due to potentially life-threatening adverse events, significant drug interactions or loss of virologic activity. Please refer to Table 5 for established and other potentially significant drug interactions.

Laboratory Tests

HCV-RNA levels should be monitored at Treatment Weeks 4, 8, 12, and 24, at the end of treatment, during treatment follow-up, and for other time points as clinically indicated. Use of a sensitive real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification of equal to or less than 25 IU/mL, and a limit of HCV-RNA detection of approximately 10-15 IU/mL. For the purposes of assessing Response-Guided Therapy milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result (reported as "target not detected" or "HCV-RNA not detected").

Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating VICTRELIS/peginterferon alfa/ribavirin combination therapy. Complete blood counts should be obtained at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.

Refer to the Package Inserts for peginterferon alfa and ribavirin, including pregnancy testing requirements.

ADVERSE REACTIONS

See peginterferon alfa and ribavirin Package Inserts for description of adverse reactions associated with their use.

Clinical Trials Experience

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

The following serious and otherwise important adverse drug reactions (ADRs) are discussed in detail in another section of the labeling:

- Anemia
- Neutropenia
- Hypersensitivity

The most commonly reported adverse reactions (>35% of subjects regardless of investigator's causality assessment) in adult subjects were fatigue, anemia, nausea, headache, and dysgeusia when VICTRELIS was used in combination with PegIntron and REBETOL.

The safety of the combination of VICTRELIS 800 mg three times daily with PegIntron/REBETOL was assessed in 2095 subjects with chronic hepatitis C in one Phase 2, open-label trial and two Phase 3, randomized, double-blind, placebo-controlled clinical trials. SPRINT-1 (subjects who were previously untreated) evaluated the use of VICTRELIS in combination with PegIntron/REBETOL with or without a four-week lead-in period with PegIntron/REBETOL compared to PegIntron/REBETOL alone. SPRINT-2 (subjects who were previously untreated) and RESPOND-2 (subjects who had failed previous therapy) evaluated the use of VICTRELIS 800 mg three times daily in combination with PegIntron/REBETOL with a four-week lead-in period with PegIntron/REBETOL compared to PegIntron/REBETOL alone. The population studied had a mean age of 49 years (3% of subjects were >65 years of age), 39% were female, 82% were white and 15% were black.

During the four week lead-in period with PegIntron/REBETOL in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL, 28/1263 (2%) subjects experienced adverse reactions leading to discontinuation of treatment. During the entire course of treatment, the proportion of subjects who discontinued treatment due to adverse reactions was 13% for subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and 12% for subjects receiving PegIntron/REBETOL alone. Events resulting in discontinuation were similar to those seen in previous studies with PegIntron/REBETOL. Only anemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm.

Adverse reactions that led to dose modifications of any drug (primarily PegIntron and REBETOL) occurred in 39% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL compared to 24% of subjects receiving PegIntron/REBETOL alone. The most common reason for dose reduction was anemia, which occurred more frequently in subjects receiving the combination of VICTRELIS with PegIntron/REBETOL than in subjects receiving PegIntron/REBETOL alone.

Serious adverse events were reported in 11% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and in 8% of subjects receiving PegIntron/REBETOL.

Adverse events (regardless of investigator's causality assessment) reported in greater than or equal to 10% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and reported at a rate of greater than or equal to 5% than PegIntron/REBETOL alone in SPRINT-1, SPRINT-2, and RESPOND-2 are presented in Table 3.

Table 3: Adverse Events Reported in ≥10% of Subjects Receiving the Combination of VICTRELIS with PegIntron/REBETOL and Reported at a Rate of ≥5% than PegIntron/REBETOL alone

Adverse Events	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Adverse Events		Percentage of Subjects Reporting Adverse Events	
Body System Organ Class	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia	50	30	45	20
Neutropenia	25	19	14	10
Gastrointestinal Disorders				
Nausea	46	42	43	38
Dysgeusia	35	16	44	11
Diarrhea	25	22	24	16
Vomiting	20	13	15	8
Dry Mouth	11	10	15	9
General Disorders and Administration Site Conditions				
Fatigue	58	59	55	50
Chills	34	29	33	30
Asthenia	15	18	21	16

Table 3: Adverse Events Reported in ≥10% of Subjects Receiving the Combination of VICTRELIS® (boceprevir) with PegIntron/REBETOL and Reported at a Rate of ≥5% than PegIntron/REBETOL alone *(continued)*

Adverse Events	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Adverse Events		Percentage of Subjects Reporting Adverse Events	
Body System Organ Class	**VICTRELIS + PegIntron + REBETOL (n=1225)**	**PegIntron + REBETOL (n=467)**	**VICTRELIS + PegIntron + REBETOL (n=323)**	**PegIntron + REBETOL (n=80)**
Median Exposure (days)	**197**	**216**	**253**	**104**
Metabolism and Nutrition Disorders				
Decreased Appetite	25	24	26	16
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	19	19	23	16
Nervous System Disorders				
Dizziness	19	16	16	10
Psychiatric Disorders				
Insomnia	34	34	30	24
Irritability	22	23	21	13
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea Exertional	8	8	11	5
Skin and Subcutaneous Tissue Disorders				
Alopecia	27	27	22	16
Dry Skin	18	18	22	9
Rash	17	19	16	6

Other Important Adverse Reactions Reported in Clinical Trials

Among subjects (previously untreated subjects or those who failed previous therapy) who received VICTRELIS in combination with peginterferon alfa and ribavirin, the following adverse drug reactions were reported. These events are notable because of their seriousness, severity, or increased frequency in subjects who received VICTRELIS in combination with peginterferon alfa and ribavirin compared with subjects who received only peginterferon alfa and ribavirin.

Gastrointestinal Disorders

Dysgeusia (alteration of taste) was an adverse event reported at an increased frequency in subjects receiving VICTRELIS in combination with peginterferon alfa and ribavirin compared with subjects receiving peginterferon alfa and ribavirin alone (Table 3). Adverse events such as dry mouth, nausea, vomiting and diarrhea were also reported at an increased frequency in subjects receiving VICTRELIS in combination with peginterferon alfa and ribavirin.

Laboratory Values

Changes in selected hematological parameters during treatment of adult subjects with the combination of VICTRELIS with PegIntron and REBETOL are described in Table 4.

Hemoglobin

Decreases in hemoglobin may require a decrease in dosage/interruption or discontinuation of ribavirin. If ribavirin is permanently discontinued, then peginterferon alfa and VICTRELIS must also be discontinued.

Neutrophils and Platelets

The proportion of subjects with decreased neutrophil and platelet counts was higher in subjects treated with VICTRELIS in combination with PegIntron/REBETOL compared to subjects receiving PegIntron/REBETOL alone. Three percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had platelet counts of less than 50 x 10^9/L compared to 1% of subjects receiving PegIntron/REBETOL alone. Decreases in neutrophils or platelets may require a decrease in dosage or interruption of peginterferon alfa, or discontinuation of therapy. If peginterferon alfa is permanently discontinued, then ribavirin and VICTRELIS must also be discontinued.

Table 4: Selected Hematological Parameters

	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Selected Hematological Parameters		Percentage of Subjects Reporting Selected Hematological Parameters	
Hematological Parameters	**VICTRELIS + PegIntron + REBETOL (n=1225)**	**PegIntron + REBETOL (n=467)**	**VICTRELIS + PegIntron + REBETOL (n=323)**	**PegIntron + REBETOL (n=80)**
Hemoglobin (g/dL)				
<10	49	29	49	25
<8.5	6	3	10	1
Neutrophils (x 10^9/L)				
<0.75	31	18	26	13
<0.5	8	4	7	4
Platelets (x 10^9/L)				
<50	3	1	4	0
<25	<1	0	0	0

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VICTRELIS in combination with peginterferon alfa and ribavirin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: mouth ulceration, stomatitis.

Skin and Subcutaneous Tissue Disorders: angioedema, urticaria; drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, exfoliative rash, exfoliative dermatitis, Stevens-Johnson syndrome, toxic skin eruption, toxicoderma.

DRUG INTERACTIONS

See also *Contraindications and Warnings and Precautions.*

Potential for VICTRELIS to Affect Other Drugs

Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS, which could increase or prolong their therapeutic and adverse effects. Boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro*. In addition, boceprevir does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Boceprevir is a potential inhibitor of p-glycoprotein (P-gp) based on in vitro studies. In a drug interaction trial conducted with digoxin, VICTRELIS had limited p-glycoprotein inhibitory potential at clinically relevant concentrations.

Potential for Other Drugs to Affect VICTRELIS® (boceprevir)

Boceprevir is primarily metabolized by aldo-ketoreductase (AKR). In drug interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, boceprevir exposure did not increase to a clinically significant extent. VICTRELIS may be coadministered with AKR inhibitors.

Boceprevir is partly metabolized by CYP3A4/5. It is also a substrate for p-glycoprotein. Coadministration of VICTRELIS with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to boceprevir.

Established and Other Potential Significant Drug Interactions

Table 5 provides recommendations based on established or potentially clinically significant drug interactions. VICTRELIS is contraindicated with drugs that are potent inducers of CYP3A4/5 and drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Table 5: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Boceprevir or Concomitant Drug	Recommendations
Antiarrhythmics: amiodarone, bepridil, propafenone, quinidine	↑ antiarrhythmics	Coadministration with VICTRELIS has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with VICTRELIS.
digoxin*	↑ digoxin	Digoxin concentrations increased when administered with VICTRELIS. Measure serum digoxin concentrations before initiating VICTRELIS. Continue monitoring digoxin concentrations; consult the digoxin prescribing information for information on titrating the digoxin dose.
Anticoagulant: warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when coadministered with VICTRELIS. Monitor INR closely.
Antidepressants: trazadone, desipramine escitalopram*	↑ trazadone ↑ desipramine ↓ escitalopram	Plasma concentrations of trazadone and desipramine may increase when administered with VICTRELIS, resulting in adverse events such as dizziness, hypotension and syncope. Use with caution and consider a lower dose of trazadone or desipramine.
Antifungals: ketoconazole*, itraconazole, posaconazole, voriconazole	↑ boceprevir ↑ itraconazole ↑ ketoconazole ↑ posaconazole ↑ voriconazole	Plasma concentrations of ketoconazole, itraconazole, voriconazole or posaconazole may be increased with VICTRELIS. When coadministration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.
Anti-gout: colchicine	↑ colchicine	Significant increases in colchicine levels are expected; fatal colchicine toxicity has been reported with other strong CYP3A4 inhibitors. Patients with renal or hepatic impairment should not be given colchicine with VICTRELIS. Treatment of gout flares (during treatment with VICTRELIS): 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout flares (during treatment with VICTRELIS): If the original regimen was 0.6 mg twice a day, reduce dose to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, reduce the dose to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF) (during treatment with VICTRELIS): Maximum daily dose of 0.6 mg (maybe given as 0.3 mg twice a day).
Anti-infective: clarithromycin	↑ clarithromycin	Concentrations of clarithromycin may be increased with VICTRELIS; however, no dosage adjustment is necessary for patients with normal renal function.
Antimycobacterial: rifabutin	↓ boceprevir ↑ rifabutin	Increases in rifabutin exposure are anticipated, while exposure of boceprevir may be decreased. Doses have not been established for the 2 drugs when used in combination. Concomitant use is not recommended.
Calcium Channel Blockers, dihydropyridine: felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Plasma concentrations of dihydropyridine calcium channel blockers may increase when administered with VICTRELIS. Caution is warranted and clinical monitoring is recommended.
Corticosteroid, systemic: dexamethasone	↓ boceprevir	Coadministration of VICTRELIS with CYP3A4/5 inducers may decrease plasma concentrations of boceprevir, which may result in loss of therapeutic effect. Therefore, this combination should be avoided if possible and used with caution if necessary.
prednisone*	↑ prednisone	Concentrations of prednisone and its active metabolite, prednisolone, increased when administered with VICTRELIS. No dose adjustment of prednisone is necessary when co-administered with VICTRELIS. Patients receiving prednisone and VICTRELIS should be monitored appropriately.
Corticosteroid, inhaled: budesonide, fluticasone	↑ budesonide ↑ fluticasone	Concomitant use of inhaled budesonide or fluticasone with VICTRELIS may result in increased plasma concentrations of budesonide or fluticasone, resulting in significantly reduced serum cortisol concentrations. Avoid coadministration if possible, particularly for extended durations.
Endothelin Receptor Antagonist: bosentan	↑ bosentan	Concentrations of bosentan may be increased when coadministered with VICTRELIS. Use with caution and monitor closely.
HIV Integrase Inhibitor: raltegravir*	⟷ raltegravir	No dose adjustment required for VICTRELIS or raltegravir.
HIV Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz*	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when VICTRELIS was coadministered with efavirenz, which may result in loss of therapeutic effect. Avoid combination.
etravirine*	↓ etravirine	Concentrations of etravirine decreased when coadministered with VICTRELIS. The clinical significance of the reductions in etravirine pharmacokinetic parameters has not been directly assessed.
HIV Protease Inhibitors: atazanavir/ritonavir*	↓ atazanavir ↓ ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir/ritonavir and boceprevir is not recommended.
darunavir/ritonavir*	↓ darunavir ↓ ritonavir ↓ boceprevir	Concomitant administration of boceprevir and darunavir/ritonavir resulted in reduced steady-state exposures to boceprevir, darunavir and ritonavir. Coadministration of darunavir/ritonavir and boceprevir is not recommended.
lopinavir/ritonavir*	↓ lopinavir ↓ ritonavir ↓ boceprevir	Concomitant administration of boceprevir and lopinavir/ritonavir resulted in reduced steady-state exposures to boceprevir, lopinavir and ritonavir. Coadministration of lopinavir/ritonavir and boceprevir is not recommended.
ritonavir*	↓ boceprevir	When boceprevir is administered with ritonavir alone, boceprevir concentrations are decreased.

Table 5: Established and Other Potentially Significant Drug Interactions *(continued)*

Concomitant Drug Class: Drug Name	Effect on Concentration of Boceprevir or Concomitant Drug	Recommendations
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ atorvastatin	Exposure to atorvastatin was increased when administered with VICTRELIS® (boceprevir). Use the lowest effective dose of atorvastatin, but do not exceed a daily dose of 40 mg when coadministered with VICTRELIS.
pravastatin*	↑ pravastatin	Concomitant administration of pravastatin with VICTRELIS increased exposure to pravastatin. Treatment with pravastatin can be initiated at the recommended dose when coadministered with VICTRELIS. Close clinical monitoring is warranted.
Immunosuppressants: cyclosporine* tacrolimus* sirolimus	↑ cyclosporine	Dose adjustments of cyclosporine should be anticipated when administered with VICTRELIS and should be guided by close monitoring of cyclosporine blood concentrations, and frequent assessments of renal function and cyclosporine-related side effects.
	↑ tacrolimus	Concomitant administration of VICTRELIS with tacrolimus requires significant dose reduction and prolongation of the dosing interval for tacrolimus, with close monitoring of tacrolimus blood concentrations and frequent assessments of renal function and tacrolimus-related side effects.
	↑ sirolimus	Blood concentrations of sirolimus are expected to increase significantly when administered with VICTRELIS. Close monitoring of sirolimus blood levels is recommended.
Inhaled beta-agonist: salmeterol	↑ salmeterol	Concurrent use of inhaled salmeterol and VICTRELIS is not recommended due to the risk of cardiovascular events associated with salmeterol.
Narcotic Analgesic/ Opioid Dependence: methadone*	↓ R-methadone	Plasma concentrations of R-methadone decreased when coadministered with VICTRELIS. The observed changes are not considered clinically relevant. No dose adjustment of methadone or VICTRELIS is recommended. Individual patients may require additional titration of their methadone dosage when VICTRELIS is started or stopped to ensure clinical effect of methadone.
buprenorphine/ naloxone*	↑ buprenorphine/ naloxone	Plasma concentrations of buprenorphine and naloxone increased when coadministered with VICTRELIS. The observed changes are not considered clinically relevant. No dose adjustment of buprenorphine/naloxone or VICTRELIS is recommended.
Oral hormonal contraceptives: drospirenone/ethinyl estradiol*	↑ drospirenone ↓ ethinyl estradiol	Concentrations of drospirenone increased in the presence of boceprevir. Thus, the use of drospirenone-containing products is contraindicated during treatment with VICTRELIS due to potential for hyperkalemia.
norethindrone/ethinyl estradiol*	↓ ethinyl estradiol ⟷ norethindrone	Concentrations of ethinyl estradiol decreased in the presence of boceprevir. Norethindrone C_{max} decreased 17% in the presence of boceprevir. Coadministration of VICTRELIS with a combined oral contraceptive containing ethinyl estradiol and at least 1 mg of norethindrone is not likely to alter the effectiveness of this combined oral contraceptive. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Increases in PDE5 inhibitor concentrations are expected, and may result in an increase in adverse events, including hypotension, syncope, visual disturbances, and priapism. Use of REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for the treatment of pulmonary arterial hypertension (PAH) is contraindicated with VICTRELIS. Use of PDE5 inhibitors for erectile dysfunction: Use with caution in combination with VICTRELIS with increased monitoring for PDE5 inhibitor-associated adverse events. Do not exceed the following doses: Sildenafil: 25 mg every 48 hours Tadalafil: 10 mg every 72 hours Vardenafil: 2.5 mg every 24 hours
Proton Pump Inhibitor: omeprazole*	⟷ omeprazole	No dose adjustment of omeprazole or VICTRELIS is recommended.
Sedative/hypnotics: alprazolam; IV midazolam	↑ midazolam ↑ alprazolam	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during coadministration of VICTRELIS. A lower dose of IV midazolam or alprazolam should be considered.

* These combinations have been studied.

USE IN SPECIFIC POPULATIONS

Pregnancy

VICTRELIS® (boceprevir) must be administered in combination with peginterferon alfa and ribavirin.

Pregnancy Category X: Use with Ribavirin and Peginterferon Alfa

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans.

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment. One of these reliable forms of contraception can be a combined oral contraceptive product containing at least 1 mg of norethindrone. Oral contraceptives containing lower doses of norethindrone and other forms of hormonal contraception have not been studied or are contraindicated.

In case of exposure during pregnancy, a Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Pregnancy Category B: VICTRELIS

VICTRELIS must not be used as a monotherapy. There are no adequate and well-controlled studies with VICTRELIS in pregnant women.

No effects on fetal development have been observed in rats and rabbits at boceprevir AUC exposures approximately 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 mg three times daily.

Nursing Mothers

It is not known whether VICTRELIS is excreted into human breast milk. Levels of boceprevir and/or metabolites in the milk of lactating rats were slightly higher than levels observed in maternal blood. Peak blood concentrations of boceprevir and/or metabolites in nursing pups were less than 1% of those of maternal blood concentrations. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with VICTRELIS, taking into account the importance of the therapy to the mother.

Pediatric Use

The safety, efficacy, and pharmacokinetic profile of VICTRELIS in pediatric patients have not been studied.

Geriatric Use

Clinical studies of VICTRELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of VICTRELIS in geriatric patients due to the greater frequency of decreased hepatic function, concomitant diseases and other drug therapy.

Renal Impairment

No dosage adjustment of VICTRELIS is required for patients with any degree of renal impairment.

Hepatic Impairment

No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment. Safety and efficacy of VICTRELIS have not been studied in patients with decompensated cirrhosis. See Package Inserts for peginterferon alfa for contraindication in hepatic decompensation.

Human Immunodeficiency Virus (HIV) Co-Infection

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection have not been established in patients co-infected with HIV and HCV.

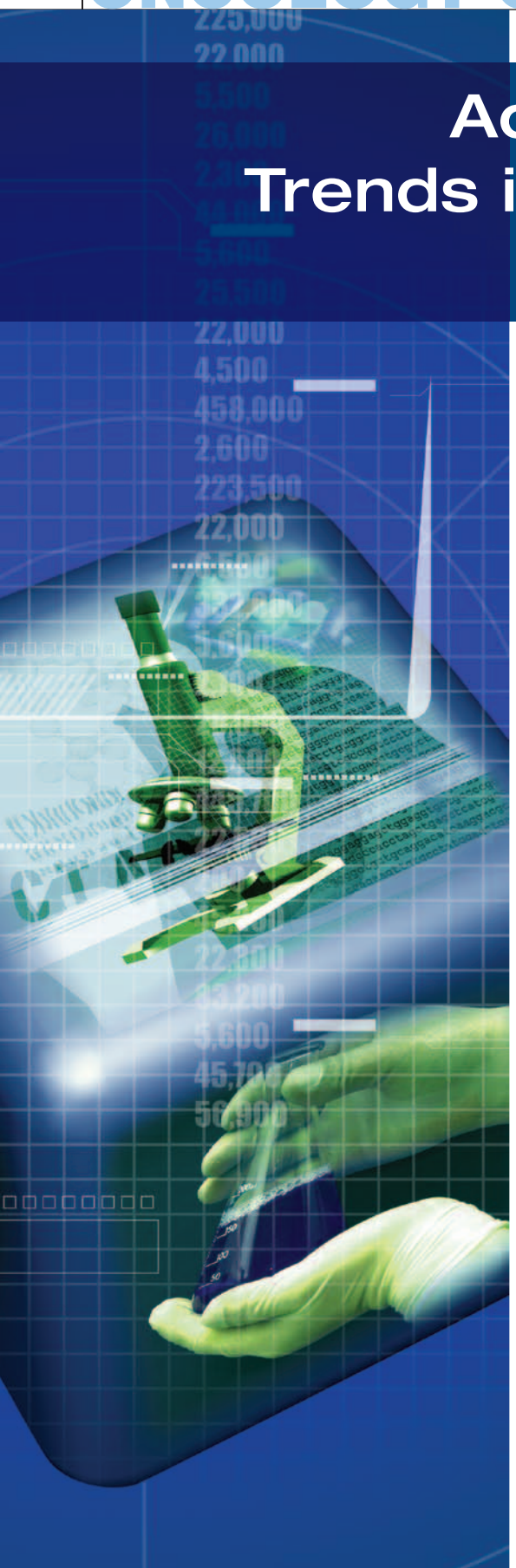
Hepatitis B Virus (HBV) Co-Infection

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with HBV and HCV have not been studied.

Organ Transplantation

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.

VICTRELIS® boceprevir 200 MG CAPSULES



Advancing Cancer Care: Trends in Quality Improvement

Maria Lopes, MD, MS, Chief Medical Officer, CDMI; and Judith Hurley, MS, RD

Maria Lopes, MD, MS

The cancer care landscape is changing rapidly and value is on the oncology front burner. Despite significant strides in some disease states, the need for more innovation, cancer prevention and improved overall survival, coupled with the need to improve the process of care and rein in high costs, is receiving a lot of attention. Fragmented care, variations in care, overutilization of cancer drugs, the evolving role of expensive new diagnostic tests and targeted therapies, and the need for more appropriate palliative and end-of-life care are particularly onerous issues facing oncology in this era of healthcare reform.[1-3] With oncology costs growing at a faster rate than healthcare costs in general and delivery systems and payment models shifting, oncology is undergoing a serious reexamination of how best to provide access to evidence-based therapies while controlling cost trends, improving care delivery, and reducing waste.

According to the health actuary company Milliman, cancer patients make up less than 1 percent of commercially insured populations, but account for 10 percent of healthcare costs.[4] The total cost of care for cancer in 2010 was $157 billion, and this is projected to increase by 39 percent—to $179 billion—by 2020.[5] The high price of chemotherapy drugs contributes substantially to these costs. Newer imaging technologies, molecular diagnostics, and expensive biologic agents are other well-recognized factors. Quality of care is heavily intertwined with cost issues. For example, patients receiving chemotherapy may experience preventable hospitalizations and emergency department visits, and shared decision-making among terminally ill patients and providers has the potential to improve quality and reduce costs, but does not always occur. This excess in healthcare utilization during end-of-life care is costly and detrimental to the patient's quality of life.[4-7]

To address both cost and quality concerns, public and private payors are increasingly linking reimbursement for cancer care to quality benchmarks.[6] The use of cancer performance metrics, clinical care pathways, enhanced care coordination, and innovations like oncology medical homes are some of the approaches being taken by health plans and oncology providers to redesign the process of cancer care.

Getting a Handle on Quality

The quality of cancer care in the United States first received widespread attention in 1999 when the Institute of Medicine released the report "Ensuring Quality Cancer Care," which described substantial care gaps that compromised patients' quality of life and survival.[8] Spurred by the report, the American Society for Clinical Oncology (ASCO) established the National Initiative for Cancer Care Quality (NICCQ), which developed quality measures for breast and colorectal cancer. In 2006, NICCQ used the measures to assess the quality of cancer care in five metropolitan areas. It found that on average, breast cancer patients received 86 percent of recommended care and colorectal cancer patients received 78 percent of recommended care.[9] However, adherence was less than 85 percent for 18 of 36 breast cancer measures and for 14 of 25 colorectal cancer measures. In addition, there was substantial variation in care across the metropolitan areas, indicating room for improvement. Problems identified were suboptimal chemotherapy dosing, inadequate management of treatment side effects, not advising patients about treatment options, and inadequate documentation of the patient's cancer and treatment.

In the past decade, cancer quality measures have been developed by several organizations, including ASCO, the American College of Surgeons (ACS) Commission on Cancer (COC), the American Medical Association's Physician Consortium for Performance Improvement (PCPI), and the National Comprehensive Cancer Network (NCCN), a consortium of 23 leading cancer centers (a sample of measures is shown in Table 1, page 50). Many performance measures are based on clinical guidelines from professional organizations. The principal domains assessed are prevention and screening, diagnostic evaluation, surgery, adjuvant therapy, management of treatment toxicity, post-treatment surveillance, and palliative care.

The Rand Corporation has developed a set of quality indicators for supportive cancer care and offers a "QA Tools" system designed to target populations vulnerable to underutilization. The system's indicators cover screening, diagnosis, treatment, and follow-up in 46 clinical areas.[10] According to NCCN, there is increasing interest in quality measures that quantify the patient experience of cancer care, such as avoidance of toxicity, length of time away from work or family, speed and completeness of recovery, and financial hardship.[11] Although important to patients, these aspects of care are not necessarily considered by providers or payors in their assessment of quality.[11]

Available performance measures can be used for internal assessment and, in some cases, benchmarking and external review. The National Quality Forum, a private sector organization that reviews and endorses standardized healthcare performance measures, currently endorses 38 cancer measures for public reporting purposes.[12] Information about many current cancer measures, including domains, target populations, and data collection details, can be accessed on the website of the National Quality Measures Clearinghouse (**www.qualitymeasures.ahrq.gov**). This comprehensive database allows for easy comparison of similar measures developed by different professional groups and organizations. Detailed measure specifications can be obtained from the individual organizations (see Table 2, page 51).

Quality Improvement Hurdles

A number of barriers to quality improvement exist. Although evidence-based guidelines developed by clinician experts have been widely adopted in the past decade, variation in adherence remains problematic

> Although there is a sizable upfront cost [to using electronic health records], the benefits to oncology practices can be substantial. Given the complexity of cancer care and the intensity of data needs, EHRs designed specifically for oncology have become available and may have advantages over generic EHRs that simply have an oncology module added on.

and this, in turn, affects quality of care. Variation in adherence may occur because guideline adoption is voluntary, assessment of adherence requires time-intensive chart abstraction when electronic health records (EHR) are not available, and the relationship between guideline adherence and long-term health outcomes has not been clearly established.[3]

Making improvements in supportive care is challenging as well. Providers may not have the resources or skills to deliver care management support and psychosocial services, and these services may not be reimbursed. While improving the patient's experience of accessing care is one of the goals of healthcare reform, assessing this domain is hampered by the inconsistent use of quality of life and satisfaction tools with patients and resulting data gaps.[3] While earlier referral for palliative care and hospice can improve end-of-life care and lead to dramatic reductions in inpatient days and ICU admissions, both patients and physicians can be reluctant to stop treatment for a number of reasons.[6] Evaluating outcomes related to optimal end-of-life care is also hindered because data for out-of-hospital deaths is not readily available.[3,4] The Coping with Cancer study, a longitudinal NIH-funded study, found that patients who participated in end-of-life discussions with their physicians had significantly lower costs in the last week of life and a better quality of life.[7] Thus, a focus on advance care planning appears to be crucial to improving both quality of care and costs. A broader concern raised by some is that current cancer performance measures are largely process-oriented and evaluate only brief segments of the care process, rather than the entire care cycle.[3]

Innovations in Cancer Care

In recent years, a number of new resources and approaches to cancer care quality have been developed. For example, the use of oncology-specific EHRs can improve adherence to guidelines and clinical pathways and facilitate gathering data for performance analysis.[13] Although there is a sizable upfront cost, the benefits to oncology practices can be substantial. Given the complexity of cancer care and the intensity of data needs, EHRs designed specifically for oncology have become available and may have advantages over generic EHRs that simply have an oncology module added on. Choosing an oncology EHR is a major task; one useful resource is KLAS Research (**www.klasresearch.com**), a company that impartially evaluates and rates EHRs in several medical specialties, including oncology.

Another trend in cancer care is the use of patient navigators. Minority and low-income populations experience disparities in cancer outcomes and increased barriers to care. Patient navigators address this by coordinating and tracking patient care, supporting patient adherence to care, and helping ensure that psychosocial and educational needs are addressed. It has been pointed out that we need to develop specific quality indicators for evaluating the impact of patient navigators on quality of care and cancer outcomes.[14]

A program that aims to integrate continuous quality improvement into patient-centered clinical practice has been developed by ASCO. Led by oncologists, the Quality Oncology Practice Initiative (QOPI) helps oncology-hematology practices improve care through performance measures, retrospective chart review, a data entry system, automated data analysis, confidential reporting, and other services and resources.[15] Data collection rounds occur twice a year and practices can then use a comparative database to identify their strengths and weaknesses. Practices meeting performance benchmarks can apply for QOPI certification. Through the QOPI Health Plan program, health plans can receive verification of an oncology practice's QOPI status.

The redesign of care in a larger context is also taking place. The concept of the medical home as a solution to fragmented care and over- or underutilization of treatment and services is gaining ground in both primary care and oncology. Key features of the medical home model are data analytics, aligned incentives, evidence-based medicine with a focus on patient-centered care, enhanced care coordination, comprehensive care, and a strengthened patient-physician relationship.[16,17] In 2010, Consultants in Medical Oncology and Hematology (CMOH), a multi-site practice in Pennsylvania, became the first oncology practice to be recognized by the National Committee for Quality Assurance (NCQA) as a level III Patient-Centered Medical Home™.[18] The CMOH Oncology Patient-Centered Medical Home Model™ incorporates coordination of care agreements with primary care practices, use of NCCN Guidelines® in developing care plans, improved documentation, an emphasis on patient engagement, a nurse triage system utilizing specific cancer care algorithms, and effective use of EHRs for managing patients and performing quality assessments.[16,18] Since 2006-2007, CMOH has seen a 68 percent reduction in emergency department visits and 51 percent reduction in hospitaliza-

tions. Through the nurse triage system, 81 percent of symptom calls initiated by patients have been able to be managed at home. Among patients triaged for closer management, the number of patients seen within 24 hours has increased by 44 percent.

Health plans are also trying out the approach. The oncology medical home demonstration project at Priority Health, a regional HMO and health insurance company based in Michigan, began in 2011 and includes six oncology practices and 60 physicians.[17] The physicians follow preferred clinical regimens for high-volume conditions and provide patient education and advance care planning. Performance metrics are used to assess compliance with clinical regimens and guidelines, per capita utilization, advance care planning, and patient experience and satisfaction. Payment reforms are an integral component. Designed to move beyond the fee-for-service model, the payment structure includes a monthly care management fee for patients receiving chemotherapy; fees for treatment planning, advance care planning, and other services; reimbursement of drug acquisition costs (rather than cost-plus reimbursement); and an annual infrastructure payment to support development of clinical information systems that will support higher quality care and quality assessment tasks. The payment structure was designed to support services not typically compensated but that are crucial to quality care, such as medication therapy management, patient education, team conferences, and psychosocial services.

Will the oncology medical home model lead to better care at a lower cost? Two proponents, David Eagle, MD, of Lake Norman Oncology in North Carolina, and John Sprandio, MD, of CMOH, wrote in the June 2011 issue of *Oncology*, "The oncology medical home has the potential to be a holistic solution to improving cancer care delivery. Instead of attempting to provide individual solutions to the problems of quality, outcome measurement, avoidance of ER visits and hospitalizations, and improved care coordination, the oncology medical home can create both the structure and process to addresses these issues simultaneously."[16]

Personalized Medicine

The advent of personalized medicine, including the use of genetic testing and biomarkers to guide use of molecular therapies, may lead to more effective treatments and improved patient survival. While choosing the right treatment for the right patient may reduce waste and cost, newer biologics are also quite expensive (the average cost of oral oncolytics is $50,000-$100,000 a year), and the net effect on overall costs is not known.[19] To be cost-effective, testing should be restricted to appropriate patients; to impact quality of care, the results must be utilized to guide treatment. In a recent survey, 93 percent of 47 health plans indicated they employ prior authorization, and often step therapy, to manage utilization of many cancer drugs.[20] However, to avoid the treatment delays associated with prior authorization, which is very problematic for patients with metastatic cancer, oncologists may decide not to use their first-choice oncolytic agent. The trade-off between managing oncolytic drug utilization—a growing trend in managed care—and providing optimal cancer care is going to be very challenging. Another quality concern related to the plethora of newer oral agents is patient adherence to the drug regimen.[19] Studies have shown that many patients fail to fill the initial prescription or continue on therapy as prescribed.[19] These and other challenging aspects of utilizing newer technologies and targeted therapies will require carefully thought out approaches. Biomarker testing guidelines for some cancers are being developed by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. An additional resource is the NCCN Biomarkers Compendium™, a tool that can be used to identify appropriate molecular testing.

Cancer Quality and Insurance Coverage

An informal survey of health insurers by the Community Oncology Alliance's Oncology Medical Home project found that health insurers consider these aspects of cancer care to be important:

- **Best possible clinical outcomes**
- **Satisfaction and positive experience for the patient**
- **Control of variable and total costs**
- **Improved survival rate and return of productivity for patients**
- **Meaningful proof of quality and value**

Source: **www.medicalhomeoncology.org**

Table 1 Sample Cancer Measures

Diagnosis
Cancer Stage Documented (American Medical Association Physician Consortium for Performance Improvement) **DESCRIPTION:** Percentage of patients, regardless of age, with a diagnosis of breast, colon, or rectal cancer who are seen in the ambulatory setting who have a baseline AJCC cancer stage or documentation that the cancer is metastatic in the medical record at least once during the 12-month reporting period.
Chronic Lymphocytic Leukemia (CLL): Baseline Flow Cytometry (American Medical Association Physician Consortium for Performance Improvement) **DESCRIPTION:** Percentage of patients ages 18 years and older with a diagnosis of CLL who had baseline flow cytometry studies performed.
Treatment
Percentage of cancer patients that received a treatment plan prior to the administration of chemotherapy (Community Oncology Alliance, Oncology Medical Home) **DESCRIPTION:** N/A
Oncology: Radiation Dose Limits to Normal Tissues (American Medical Association Physician Consortium for Performance Improvement) **DESCRIPTION:** Percentage of patients, regardless of age, with a diagnosis of pancreatic or lung cancer who receive 3-D conformal radiation therapy with documentation in medical record that radiation dose limits to normal tissues were established prior to the initiation of a course of 3-D conformal radiation for a minimum of two tissues.
Adjuvant Hormonal Therapy (Commission on Cancer, American College of Surgeons) **DESCRIPTION:** Percentage of female patients, age >18 at diagnosis, who have their first diagnosis of breast cancer (epithelial malignancy), at AJCC stage I, II, or III, whose primary tumor is progesterone or estrogen receptor positive and recommended for tamoxifen or third-generation aromatase inhibitor (considered or administered) within 1 year (365 days) of diagnosis.
Adjuvant chemotherapy is considered or administered within four months (120 days) of surgery to patients under the age of 80 with AJCC III (lymph node positive) colon cancer (Commission on Cancer, American College of Surgeons) **DESCRIPTION:** Percentage of patients under the age of 80 with AJCC III (lymph node positive) colon cancer for whom adjuvant chemotherapy is considered or administered within 4 months (120 days) of diagnosis.
Palliative/End-of-Life
Proportion admitted to the ICU in the last 30 days of life (American Society of Clinical Oncology) **DESCRIPTION:** Percentage of patients who died from cancer admitted to the ICU in the last 30 days of life.
Proportion not admitted to hospice (American Society of Clinical Oncology) **DESCRIPTION:** Percentage of patients who died from cancer not admitted to hospice.
Proportion receiving chemotherapy in the last 14 days of life (American Society of Clinical Oncology) **DESCRIPTION:** Percentage of patients who died from cancer receiving chemotherapy in the last 14 days of life.
Percentage of patients that have Stage IV disease that have end-of-life care discussions documented (Community Oncology Alliance, Oncology Medical Home) **DESCRIPTION:** N/A
Resource Utilization
Number of emergency room visits per chemotherapy patient per year (Community Oncology Alliance, Oncology Medical Home) **DESCRIPTION:** N/A
Number of hospital admissions per chemotherapy patient per year (Community Oncology Alliance, Oncology Medical Home) **DESCRIPTION:** N/A
N/A, not available

Table 2 Resources in Cancer Care Quality

Organization	Resource	For More Information
	QUALITY MEASURES	
COA	Quality measures for oncology medical homes	**www.medicalhomeoncology.org/coa/benchmarking.htm**
COC	Quality measure set	Cancer Program Standards 2009 Revised Edition: **www.facs.org/cancer/coc/programstandards.html** Cancer Program Standards 2012 Version 1.1: Ensuring Patient Centered Care: **www.facs.org/cancer/coc/standards.html**
NQMC	Database of quality measure sets from multiple organizations/developers	**www.qualitymeasures.ahrq.gov**
PCPI	Quality measure set	**www.ama-assn.org/apps/listserv/x-check/qmeasure.cgi?submit=PCPI**
RAND	Cancer Quality-ASSIST Project quality indicators for supportive care	**www.effectivehealthcare.ahrq.gov/ehc/products/190/444/finalforposting%20DECIDE%2024.pdf**
	BEST PRACTICES	
ASCO	Cancer quality guidelines	**www.asco.org/institute-quality/guidelines**
QOPI	Practice-Based Quality Improvement program	**http://qopi.asco.org/**
COC	COC Best Practices Repository: sample documents and tools	**www.socialtext.net/cancer_standards/coc%20best%20practices%20repository**
NAPBC	NAPBC Standards	**http://napbc-breast.org/standards/standards.html**
NCQA	Patient-Centered Medical Home program	**www.ncqa.org/Programs/Recognition/PatientCenteredMedicalHomePCMH.aspx**
	ANALYSIS TOOLS	
NCCN	Analytics tools, oncology outcomes database, reimbursement resources, cancer drug compendium, cancer biologics compendium	**www.nccn.org**
RAND	QA Tools System, Oncology	**www.rand.org/health/surveys_tools/qatools.html**

ACS, American College of Surgeons
PCPI, Physician Consortium for Performance Improvement, American Medical Association
ASCO, American Society of Clinical Oncology
COA, Community Oncology Alliance
COC, Commission on Cancer, American College of Surgeons
NAPBC, National Accreditation Program for Breast Centers
NCCN, National Comprehensive Cancer Network
NQMC, National Quality Measures Clearinghouse
QOPI, Quality Oncology Practice Initiative

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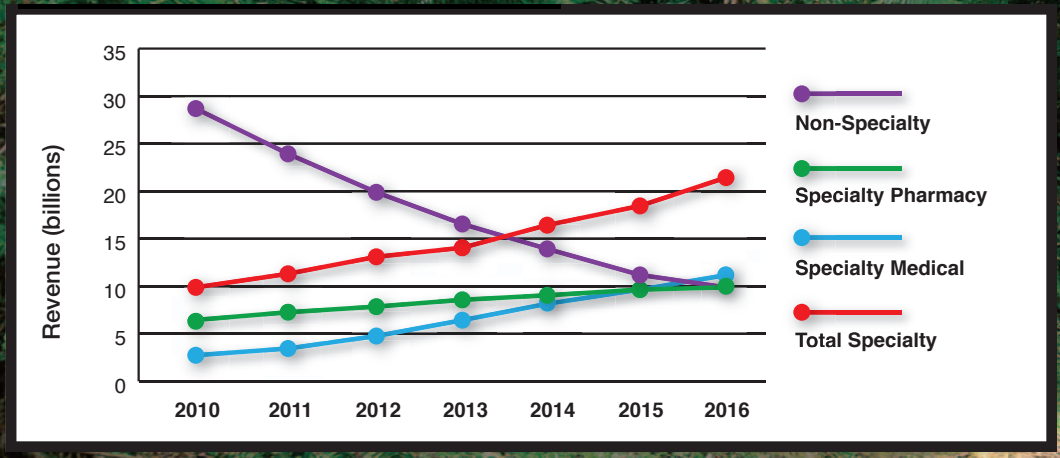


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Persistence and Discontinuation
Among Newly Initiated Kinase Inhibitor Treated Patients for One Year Post Initiation

The emergence of tyrosine kinase inhibitors (TKIs) changed the treatment approach for certain cancers and significantly improved patient survival over the past decade. TKIs are a growing class of small-molecule medications aimed at inhibiting critical kinases implicated in perpetuating cancer growth.[1] Now that multiple kinase inhibitors are available, patients, clinicians, and managed care organizations (MCOs) can weigh relative advantages, toxicities, and costs when selecting treatment options. An additional important piece of information that can weigh into decision making is persistence, discontinuation, and adherence to TKIs. In this analysis, we chose to examine what occurs with a newly initiated health plan patient within the first year of treatment among select TKIs.

Our objective for this analysis was to identify newly initiated (TKI-naïve) patients to understand persistence, discontinuation, and adherence over the first year of therapy. To do so, pharmacy claims data from a large regional health plan was used containing approximately 1.3 million lives. All health plan claims were accessed in a fully Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. All continuously enrolled (CE) health plan patients (>18 years of age) newly initiated on a select TKI (Table 1) between January 1, 2010, and December 31, 2011, were identified. Patients identified as newly initiated were continuously enrolled six months prior to their first TKI claim. Patients were assumed to discontinue therapy if they were continuously enrolled and had a gap in therapy of more than 30 days following the expected completion of their last TKI prescription. Patients identified as persistent did not discontinue TKI therapy after initiation. Proportion of days covered (PDC) was used as a measure of adherence.

A total of 234 TKI patients were identified that newly initiated therapy with data available for one year thereafter: mean age: 56.6, female: 43.6 percent. Of the 234 TKI patients, 1 (0.43 percent) patient discontinued by month three, 42 (18.0 percent) discontinued by month six, and 48 (20.5 percent) discontinued by month nine, with an average duration of first-line TKI therapy of 182.7 days. Twenty patients (8.6 percent) switched therapy to a second oncology agent, and two patients (0.85 percent) went on to a third treatment during the measurement year. One hundred and sixty-six patients (70.9 percent) remained persistent for at least one year post-TKI initiation. Of those patients who remained persistent, mean adherence (PDC) was 79.4 percent, and patients had an average maximum gap in therapy of 32.1 days.

This analysis holds some important limitations. We did not take indications into account when analyzing the data. Additionally, this analysis is not meant to be comparative. A goal was to identify if a gap in care exists for those patients treated with TKIs.

TKIs are a novel treatment that significantly impacted the approach to therapy for certain cancers. A majority of patients (70.9 percent) remained persistent on their

medication for the first year of therapy. However, due to the safety, tolerability, cost, and importance of taking these therapies as prescribed, there is an opportunity for MCOs to improve patient persistency and adherence and reduce gaps in therapy.

Table 1

Select Tyrosine Kinase Inhibitors[1]

Product	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range
Imatinib (Gleevec)	Tablet: 100 mg, 400 mg	Treatment of gastrointestinal stromal tumors (GIST) kit-positive (CD117), including unresectable and/or metastatic malignant and adjuvant treatment following complete resection; Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (newly diagnosed) Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon therapy; Ph+ acute lymphoblastic leukemia (ALL) (relapsed or refractory); aggressive systemic mastocytosis (ASM) without D816V c-Kit mutation (or c-Kit mutation status unknown); dermatofibrosarcoma protuberans (DFSP) (unresectable, recurrent, and/or metastatic); hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia; (CEL); myelodysplastic/myeloproliferative disease (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements	Treatment of desmoid tumors or chordoma (soft tissue sarcomas); post-stem cell transplant (allogeneic) follow-up treatment for recurrence in CML; treatment of Ph+ acute lymphoblastic lymphoma	600-800 mg/day (800 mg/day should be dosed 400 mg twice daily)
Axitinib (Inlyta)	Capsule: 200 mg, 250 mg	Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase positive (as detected by an FDA-approved test)	N/A	250 mg twice daily
Sorafenib (Nexavar)	Tablet: 200 mg	Treatment of advanced renal cell cancer (RCC); treatment of unresectable hepatocellular cancer (HCC)	Treatment of advanced thyroid cancer, recurrent or metastatic angiosarcoma, resistant gastrointestinal stromal tumor (GIST)	400 mg twice daily
Dasatinib (Sprycel)	Tablet: 20 mg, 50 mg, 70 mg, 100 mg	Treatment of chronic myelogenous leukemia (CML) in chronic, accelerated, or blast (myeloid or lymphoid) phase resistant or intolerant to prior therapy (including imatinib); treatment of newly diagnosed Philadelphia chromosome-positive (Ph+) CML in chronic phase; treatment of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to prior therapy	Post-stem cell transplant (allogeneic) follow-up treatment of CML; treatment of gastrointestinal stromal tumor (GIST)	140-180 mg once daily
Sunitinib (Sutent)	Capsule: 12.5 mg, 25 mg, 50 mg	Treatment of gastrointestinal stromal tumor (GIST) intolerant to or with disease progression on imatinib; treatment of advanced renal cell cancer (RCC); treatment of advanced, metastatic, or unresectable pancreatic neuroendocrine tumors (PNET)	Treatment of advanced thyroid cancer; treatment of non-GIST soft tissue sarcomas	37.5-50 mg once daily
Erlotinib (Tarceva)	Tablet: 25 mg, 100 mg, 150 mg	Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) refractory to at least one prior chemotherapy regimen (as monotherapy); maintenance treatment of locally advanced or metastatic; NCSLC that has not progressed after 4-6 cycles of first-line platinum-based chemotherapy; locally advanced, unresectable, or metastatic pancreatic cancer (first-line therapy in combination with gemcitabine)	First-line treatment of NSCLC with known EGFR mutation; treatment of head and neck cancer	100-300 mg once daily
Nilotinib (Tasigna)	Capsule: 150 mg, 200 mg	Treatment of newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in chronic phase; treatment of chronic and accelerated phase Ph+ CML refractory or intolerant to prior therapy (including imatinib)	Treatment of refractory gastrointestinal stromal tumor (GIST)	200-400 mg twice daily
Pazopanib (Votrient)	Tablet: 200 mg	Treatment of advanced renal cell cancer (RCC); treatment of advanced soft tissue sarcoma (STS) (in patients previously treated with chemotherapy)	Treatment of advanced differentiated thyroid cancer	400-800 mg once daily

Table 2

Basic Demographics (Single-Drug Patients)

Drug Name	N	%	Female	%	Age
Gleevec	99	46.7%	39.0	41.9%	53.1
Nexavar	18	8.5%	6.0	6.5%	57.8
Sprycel	7	3.3%	2.0	2.2%	50.7
Sutent	23	10.8%	7.0	7.5%	61.0
Tarceva	45	21.2%	32.0	34.4%	60.6
Tasigna	12	5.7%	5.0	5.4%	52.1
Votrient	8	3.8%	2.0	2.2%	62.5
Total	**212**	**100.0%**	**93.0**	**43.9%**	**56.6**

Table 3

Overall Persistence on TKI Therapy

Patients discontinuing therapy by:	N	%
3 months	1	0.43%
6 months	42	18.0%
9 months	48	20.5%
12 months	68	29.1%
Patients that switched to:		
1 additional TKI	20	8.6%
2 additional TKIs	2	0.9%

Reference

1. Archer M, et al. Drug class review: Antineoplastic tyrosine kinase inhibitors. September 2012. University of Utah College of Pharmacy.

PIPELINE TRENDS

NEW DRUG APPROVALS

Drug	Manufacturer	Approval Date	Indication
Rixubis™ (coagulation factor IX [recombinant]) injection	Baxter	June 26, 2013	Antihemophilic factor indicated for the control and prevention of bleeding episodes in adults with hemophilia B
Brisdelle™ (paroxetine) capsule	Noven	June 28, 2013	Selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause
Zubsolv™ (buprenorphine/ naloxone) sublingual tablet	Orexo	July 3, 2013	Partial opioid agonist indicated for the maintenance treatment of opioid dependence
Khedezla™ (desvenlafax-ine) extended-release tablet	Osmotica	July 10, 2013	Serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder
Gilotrif™ (afatinib) tablet	Boehringer Ingelheim	July 12, 2013	Kinase inhibitor for first-line treatment for patients with metastatic non-small cell lung cancer with common epidermal growth factor receptor mutations
Astagraf XL™ (tacrolimus) extended-release capsule	Astellas	July 19, 2013	Calcineurin-inhibitor immunosuppressant indicated for prophylaxis of organ rejection in patients receiving kidney transplant
Lo Minastrin™ Fe (norethindrone acetate, ethinyl estradiol ferrous fumarate) tablet	Warner Chilcott	July 24, 2013	Estrogen/progestin combined oral contraceptive
Fetzima™ (levomilnacipran) extended-release capsule	Forest	July 25, 2013	Serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder
Injectafer® (ferric carboxy-maltose) injection	Luitpold	July 25, 2013	Iron replacement product indicated for the treatment of iron deficiency anemia

NEW FDA-APPROVED INDICATIONS

Drug	Approval Date	Indication
Xgeva® (denosumab)	June 13, 2013	Indicated for treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable
Vibativ® (telavancin)	June 21, 2013	Expanded approved use to treat patients with hospital-acquired and ventilator-associated bacterial pneumonia
Exelon® (rivastigmine)	June 27, 2013	Expanded approval to treat patients with severe Alzheimer's disease
Latuda® (lurasidone HCl)	June 28, 2013	Approved as monotherapy and adjunctive therapy with lithium or valproate to treat adult patients with major depressive episodes associated with bipolar I disorder

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

NEW FORMULATIONS AND DOSAGE FORMS		
Drug	**Approval Date**	**Advertised Advantage**
Simponi® Aria™ (golimumab) Infusion	July 18, 2013	30-minute infusion given at week 0, 4 and every 8 weeks thereafter for treatment of adults with moderately to severely active rheumatoid arthritis (RA)

NEW FIRST-TIME GENERIC DRUG APPROVALS
Voriconazole (Vfend®) oral suspension, approved: May 28, 2013
Rasagiline (Azilect®) tablet, approved: July 1, 2013
Decitabine (Dacogen®) injection, approved: July 11, 2013
Repaglinide (Prandin®) tablet, approved: July 11, 2013
Acamprosate calcium (Campral®) delayed-release tablet, approved: July 16, 2013

HEMOPHILIA PIPELINE					
Manufacturer	**Hemophilia Type**	**Phase 1**	**Phase 2**	**Phase 3**	**Filed with FDA**
CSL Behring	A/B	rVIIa-FP			
Novo Nordisk	A/B	Monoclonal Antibody			
Baxter	A		Long-acting rFVIII		
Bayer	A		Pegylated rFVIII		
Bayer	A		rFVIIIa		
CSL Behring	A		rVIII Single Chain		
CSL Behring	B		rIX-FP		
Novo Nordisk	A		Long-acting rFVIII derivative		
Novo Nordisk	B		Long-acting rFIX derivative		
Octapharma	A		Human-cl rhFVIII		
Biogen	A		rFVIII		
Biogen	B		rFIX		
Cangene	B		rFIX		
Novo Nordisk	A		rFVIII		

LOOKING FORWARD AT HEMOPHILIA TREATMENT

The development of longer-acting and more potent clotting factors has the potential for major improvements in the current standards of hemophilia care. Longer-acting products may reduce the frequency of infusions, greatly increasing patient convenience. More potent products may be critical to care for patients with inhibitors, in whom traditional therapy is not as effective.

COMING SOON …			
Drug	**Manufacturer**	**Proposed Indication**	**PDUFA Date**
Otrexup™ (methotrexate)	Antares Pharma, Inc.	Subcutaneous self-injection of methotrexate using Medi-Jet™ technology to enhance treatment of RA and psoriasis	October 14, 2013
Opsumit® (macitentan)	Actelion	Dual endothelin receptor antagonist for treatment of pulmonary arterial hypertension	October 19, 2013
Sofosbuvir	Gilead Sciences, Inc.	Once-daily oral nucleotide analogue inhibitor for treatment of chronic HCV	December 8, 2013
Anoro™ (UMEC/VI)	GlaxoSmithKline and Theravance	LAMA/LABA combination for treatment of COPD	December 18, 2013
Miltefosine	Paladin Labs Inc.	Oral agent for treatment of leishmaniasis	December 19, 2013

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More detailed information is available upon request.

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

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

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VICTOZA®
liraglutide (rDNA origin) injection

PROVEN.

LOW RATE OF HYPOGLYCEMIA

POWERFUL A1C REDUCTIONS
-0.8% to -1.5%*

MAY PROVIDE ADDITIONAL BENEFIT OF WEIGHT LOSS†

For adult patients with type 2 diabetes, Victoza® offers these benefits and more.
Visit **VictozaPro.com/Care** to learn how the support program helps patients get started.

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*Victoza® 1.2 mg and 1.8 mg when used alone or in combination with OADs.
†**Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials.**

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® (liraglutide [rDNA origin] injection) 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.

Please see brief summary of Prescribing Information on adjacent page.

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