Summer 2013

Gaucher Disease: Managed Care Implications

Managing Hereditary Angiodema

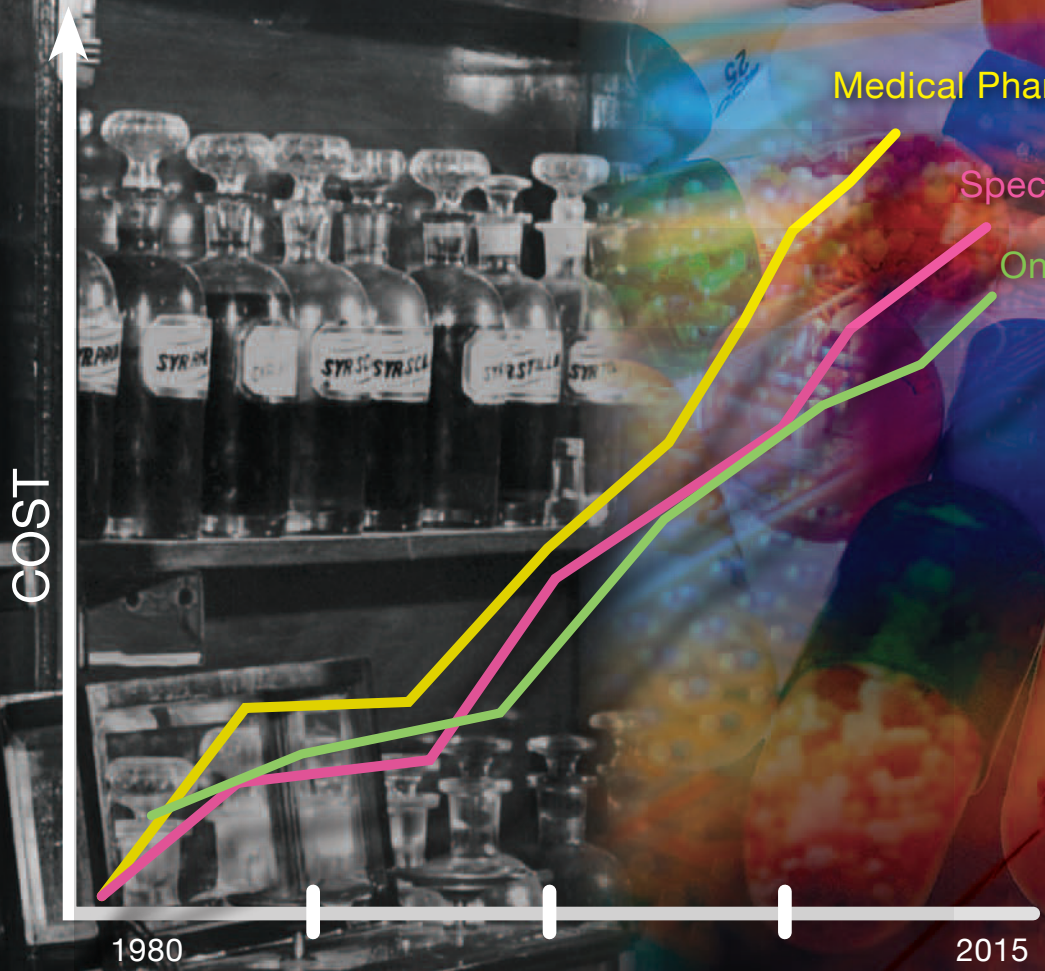
Neurotoxins: A Clinical and Financial Outlook

Antiplatelet Therapy for ACS

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Past vs. Present New Generation of Specialty Management



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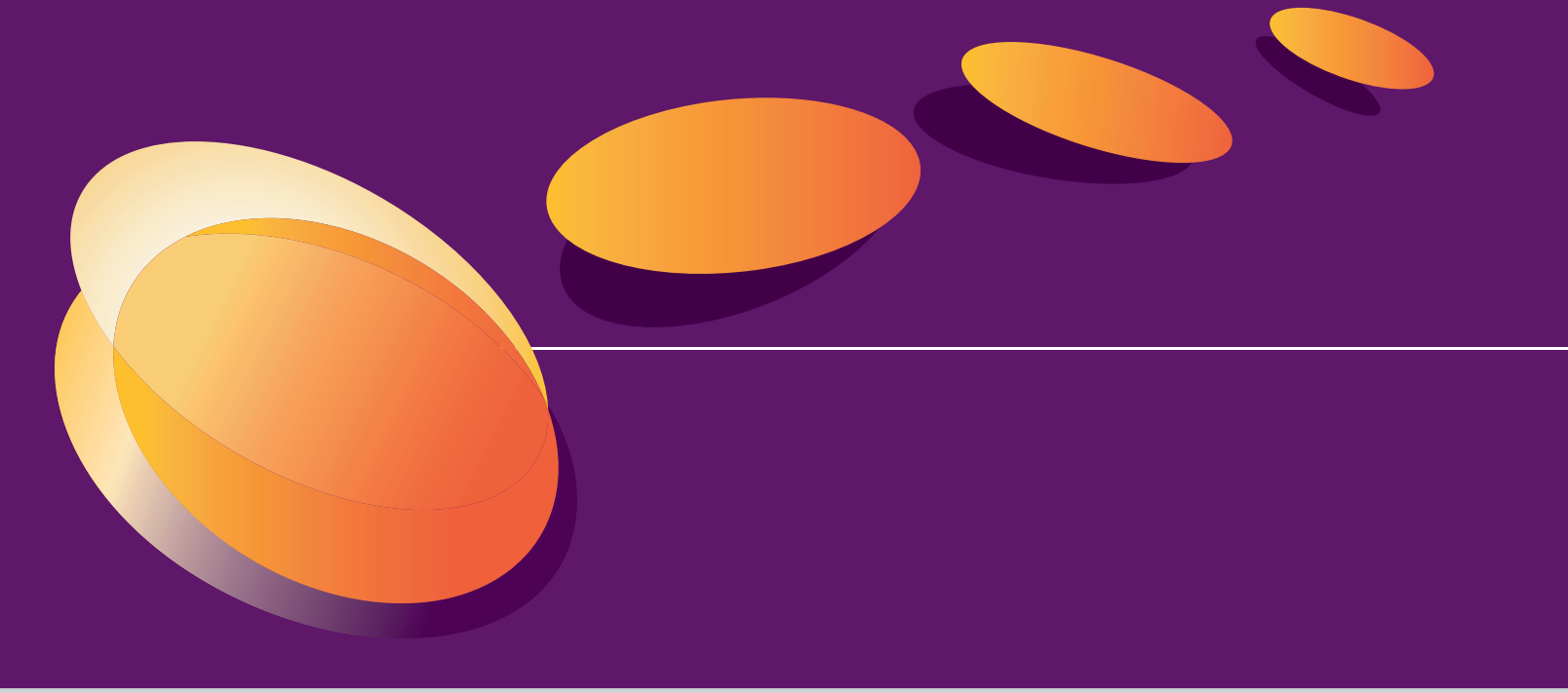


BRILINTA plus aspirin significantly reduced the primary composite end point of CV death, myocardial infarction (MI),* or stroke by 16% RRR† (ARR‡ 1.9%) vs clopidogrel plus aspirin at 12 months§

At 12 months, for BRILINTA plus aspirin vs clopidogrel plus aspirin, there was no significant difference in Total Major Bleeding (11.6% vs 11.2%) and a somewhat greater risk of Non–CABG-related Major plus Minor Bleeding (8.7% vs 7.0%) and Non–CABG-related Major Bleeding (4.5% vs 3.8%), respectively

INDICATIONS

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

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

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

Please read additional Important Safety Information on next page and Brief Summary of Prescribing Information, including Boxed WARNINGS, on following pages.

In the treatment of acute coronary syndrome (ACS)

BRILINTA provided superior reductions versus clopidogrel in thrombotic CV events, including CV death

The difference between treatments was driven by CV death and MI with no difference in stroke

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

*Excluding silent MI.

†RRR=relative risk reduction.

‡ARR=absolute risk reduction.

§The PLATO (PLATelet Inhibition and Patient Outcomes) study was a randomized, double-blind, parallel-group trial comparing 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 admitted to the hospital within 24 hours of symptom onset of ACS (UA [unstable angina], NSTEMI [non–ST-elevation MI], or STEMI [ST-elevation MI]). Patients were treated for at least 6 months and up to 12 months. BRILINTA and clopidogrel were studied with aspirin and other standard therapies.

For more information, go to BRILINTAtouchpoints.com

Reference: BRILINTA Prescribing Information, AstraZeneca.

BRILINTA®
ticagrelor tablets

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*]

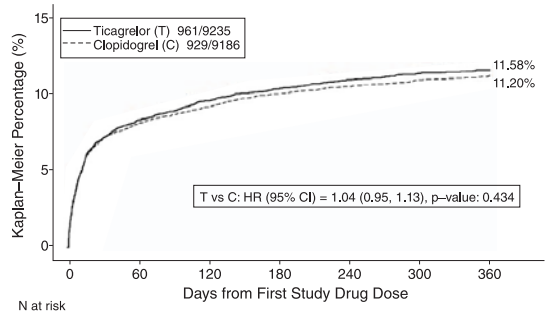
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety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

Issued: March 29, 2013

Distributed by: AstraZeneca LP, Wilmington, DE 19850

Rev. 3/13 2574902 4/13

AstraZeneca

CDMI REPORT

ISSN: 2159-5372

PUBLISHED BY:
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WELCOME

to this issue

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trends

Letter from the President

Susan Petrovas

Dear Managed Care Colleagues,

Susan Petrovas, RPh, President

As specialty pharmaceuticals are quickly overtaking traditional medications in terms of total costs, developing appropriate strategies to manage these complex conditions is becoming critical for healthcare sustainability. To help alleviate the burden placed on health plans, CDMI has been working with our customers to develop clinically based and cost-effective solutions to address the dynamic changes occurring within the specialty market. These solutions include appropriate strategies to manage the influx of expensive and orally administered products in multiple sclerosis, rheumatoid arthritis, and oncology—an area of increasing interest.

In addition to these extremely costly specialty disease states, CDMI is creating opportunities for health plans to experience cost-savings in a variety of other disease states through the use of appropriate clinical management strategies. Examples of our recent developments include:

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

- Site-of-care and dose optimization programs to control costs associated with immune globulin therapy and neurotoxins
- Appropriate use of prophylaxis therapy in patients with hereditary angioedema (HAE) or hemophilia
- HIV and hepatitis C adherence and persistence support services

To ensure all our specialty management solutions follow the utmost standards of clinical practice, CDMI works with world-renowned specialists in the development of each component. Through working with these key opinion leaders, as well as trusted managed care executives, CDMI has developed a wide variety of specialty management services to improve the quality of care delivered by our payor customers. These solutions can be customized based on specific plan needs and include formulary management and compliance, adherence and persistency programs, clinical pathways of care, quality performance improvement programs, site-of-care optimization, and care coordination improvement programs.

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

Sincerely,

Susan C. Petrovas, R.Ph
President, CDMI

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MANAGED CARE NEWSSTAND

New Study Finds No Significant Increased Cancer Risk in Women Who Undergo IVF

A new study found no significant increased risk for breast, endometrial, or ovarian cancers in women who underwent in vitro fertilization (IVF) when compared with women who were evaluated for infertility but who never had IVF. Researchers evaluated the medical records of more than 87,000 Israeli women and followed them for cancer development for a period of 17 years. They found no significant increased cancer risk among the women who had IVF during the study period. However, the researchers noted that there was a very slight increase in the risk for ovarian cancer in women who underwent IVF when compared to those who had no fertility treatments. The risk was higher in women who had four or more cycles.

The researchers say their findings may provide some reassurance about the association between IVF and cancer. They say, however, that women who undergo IVF should continue to be monitored because IVF treatment includes the use of potent medications to stimulate ovulation and repeated puncturing of the ovaries.

Source: Brinton L, et al. In vitro fertilization and risk of breast and gynecologic cancers: A retrospective cohort study within the Israeli Maccabi Healthcare Services. *Fertility and Sterility.* 2013;99(5):1189-1196.

New Drug May Target Leukemia Stem Cells

Researchers in California have found that sabutoclax, an investigational compound, may target certain drug-resistant leukemia stem cells (LSCs) selectively—a finding that could lead to improved combination treatments for diseases such as chronic myeloid leukemia (CML) and some solid-tumor cancers.

Tyrosine kinase inhibitors (TKIs) are emerging as a popular cancer treatment. But these medications are not always effective. In patients with CML, for example, some LSCs in the bone marrow can avoid destruction, become resistant to these drugs, and self-renew. Eventually, patients may suffer a relapse. However, the LSCs in the bone marrow that overexpress several pro-survival proteins appear to be vulnerable to sabutoclax. The researchers note that sabutoclax, in combination with other therapies, may eventually offer a new and effective treatment option that may reduce the risk for relapse.

Source: Goff D, et al. A Pan-BCL2 inhibitor renders bone-marrow-resident human leukemia stem cells sensitive to tyrosine kinase inhibition. *Cell Stem Cell.* 2013;12(3):316-328.

Studies Provide New Data About the Use of Factor VIII Products for Hemophilia

Separate groups of researchers reported important findings about factor VIII products for patients with the bleeding disorder hemophilia. Results from the largest phase 3 registrational studies on hemophilia to date were presented at the 6th Annual Congress of the European Association for Haemophilia and Allied Disorders in February 2013. Researchers confirmed that investigational factors VIII Fc fusion protein (rFVIIIFc) and IX Fc fusion protein (rFIXFc) provide long-lasting protection from bleeding while requiring fewer injections. The studies evaluated the effectiveness of rFVIIIFc for hemophilia A and rFIXFc for hemophilia B. Patients with hemophilia A maintained low bleeding rates with one or two weekly prophylactic injections of rFVIIIFc, while those with hemophilia B had low bleeding rates with prophylactic injections of rFIXFc every one to two weeks.

Other researchers reported the results of their study of different factor VIII products in children with severe hemophilia A who were previously untreated. They found that the risks of inhibitor development (defined as at least two positive inhibitor tests with reduced in vivo recovery of factor VIII levels) were similar for both recombinant and plasma-derived factor VIII products. There was no increased risk in products that contained the von Willebrand factor or when patients switched products. However, the risk was higher in second-generation full-length recombinant products when compared with third-generation products.

Sources:
New phase 3 date reinforce long-lasting protection from bleeding for patients with hemophilia A and B. 6th Annual Congress of the European Association for Haemophilia and Allied Disorders. Feb. 2013. News release.

Gouw S, et al. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med.* 2013;368:231-239.

RA Costs Employers Nearly $6 Billion

Researchers say nearly $6 billion is spent in direct and indirect costs to treat workers who have rheumatoid arthritis (RA). As part of a study published in the *Journal of Occupational and Environmental Medicine,* researchers compared employer costs for more than 2,700 workers who had RA with nearly 340,000 workers without RA. They found that the average annual cost for workers with RA was $5,200 higher than it was for employees without RA ($8,700 for those with RA and $3,500 for those without RA). The majority—90 percent—of the excess costs for RA workers was due to direct healthcare costs. But workers with RA also incurred higher indirect costs. They, for example, took an average of 3.5 additional days off per year for health-related reasons. This included more sick and short-term disability time. Based on their findings, the researchers estimated that RA costs employers $5.8 billion in direct and indirect costs and 4 million lost work days each year.

This study highlights the importance of developing effective management strategies to help patients with RA maximize control of their disease and reduce economic losses.

Source: Kleinman N, et al. Annual incremental health benefit costs and absenteeism among employees with and without rheumatoid arthritis. *J Occup Environ Med.* 2013;55(3):240-4.

Positive Data from Study of Oral Therapy for Type 1 Gaucher Disease

Phase 3 studies of an investigational oral substrate synthesis inhibitor, eliglustat tartrate, for Type 1 Gaucher disease met researchers' primary efficacy end points. Results of the phase 3 ENGAGE trial were presented at a February 2013 symposium. Genzyme, the company developing eliglustat tartrate, released results of the ENCORE trial in conjunction with the symposium.

ENGAGE was a randomized, double-blind, placebo-controlled study that included 40 treatment-naïve patients with Type 1 Gaucher disease. Researchers noted improvements in all primary and secondary efficacy end points during the nine-month study period. Participants experienced a statistically significant improvement in spleen size—the primary efficacy end point. Spleen volume decreased 28 percent from baseline in those treated with eliglustat tartrate, while it increased a mean of 2 percent in the placebo group.

The ENCORE trial was designed to compare eliglustat tartrate with injectable imiglucerase (Cerezyme®). This study also met its primary efficacy end point and will be reported later this year. According to Genzyme, its clinical development program, which includes about 400 patients in 30 countries, is the largest clinical program to date for Type 1 Gaucher disease.

This medication has the potential to broaden the treatments available for Type 1 Gaucher disease and offer patients a more convenient therapeutic option.

Source: 9th Annual Lysosomal Disease Network WORLD Symposium. Feb. 2013. News release.

Researchers Identify Possible New Drug Target for MS and AD

Researchers at Boston University School of Medicine have found that the protein klotho plays a key role in the health of myelin. It was reported in the *Journal of Neuroscience* that adding klotho to immature myelin-producing cells (oligodendrocytes) causes the cells to mature and produce proteins needed for healthy myelin. The researchers also identified molecules that could lead to the development of new drugs to increase klotho levels in the brain. Previously, these researchers found that klotho levels in the brain decline and myelin abnormalities increase with age.

Their findings could play a role in treating white-matter diseases, such as multiple sclerosis and Alzheimer's disease. Drugs that increase klotho levels may help protect the brain against age-related changes in the myelin and even promote repair.

Source: Chen C, et al. The antiaging protein klotho enhances oligodendrocyte maturation and myelination of the CNS. *J Neurosci.* 2013;33(5):1927-1939.

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.

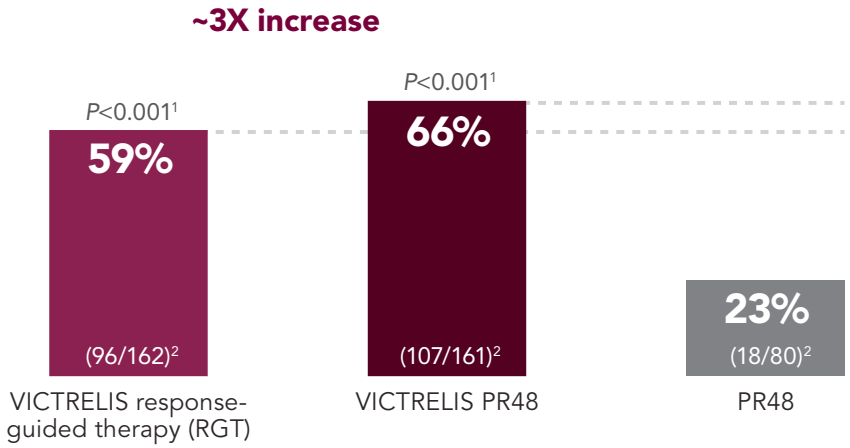
VICTRELIS® boceprevir 200 MG CAPSULES

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 digoxin*	↑ antiarrhythmics ↑ digoxin	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 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 prednisone*	↓ boceprevir ↑ prednisone	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. 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* etravirine*	↓ boceprevir ↓ etravirine	Plasma trough concentrations of boceprevir were decreased when VICTRELIS was coadministered with efavirenz, which may result in loss of therapeutic effect. Avoid combination. 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

Gaucher Disease:
Managed Care Implications

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Gaucher disease (GD) is a rare, heritable lysosomal glycosphingolipid storage disorder.[1] GD is caused by germline genetic mutations that lead to absent or reduced glucocerebrosidase activity with resultant accumulation of the primary substrate, glucocerebroside, throughout the body, but especially in the liver, spleen, bones, and bone marrow.[1] There are three main GD subcategories, with Type 1 being the most prevalent in the Western world.[1,2] Patients with Type 1 disease generally have no clinically evident central or peripheral nervous system involvement until late adulthood, when some may develop peripheral neuropathy or Parkinson's-like manifestations.[1] When the disorder is left untreated, actuarial life expectancy is shorter in patients with Type 1 GD than in the general population.[3] Type 2 is the least prevalent and is characterized by aggressive and inexorable neuronopathic onset in infancy and death generally by 2 to 3 years of age.[1] Variable neuronopathic features are also seen in Type 3 disease; however, some patients have only mild to minimal functional and intellectual impairment and may live well into adulthood, provided that systemic manifestations of GD are effectively treated.[1] GD occurs in patients of Ashkenazi Jewish heritage at a prevalence of about 1 in 600 people, compared to 1 in 57,000 to 150,000 people in non-Ashkenazi populations.[1,2]

GD has many phenotypic variants and a range of presentations with different clinical severity and age of onset.[1,2] Systemic manifestations variably found in all GD subtypes include hepatomegaly and splenomegaly, hematological abnormalities (anemia with associated fatigue and thrombocytopenia with bleeding complications), bone disease (osteopenia, fractures, necrosis, joint destruction, acute and chronic pain), and growth and sexual developmental delay. Lung involvement is unusual but highly ominous when present. CNS manifestations found in patients with Types 2 and 3 include ocular abnormalities (ophthalmic apraxia, strabismus), palsy, hypertonia, rigidity, seizures, and severe kyphosis with gibbus formation.[1,4] Type 1 GD patients may appear to be asymptomatic but are nevertheless commonly found to have significant disease mani-

festations when they are carefully and comprehensively evaluated.[1] Disease status has also been demonstrated to negatively impact patient quality of life in home, social, school, and work situations.[1,5,6,7]

Disease Management

Treatment should be started in all symptomatic patients and if morbidities such as skeletal manifestations are already present. Furthermore, treatment should be initiated early in cases where, based on genotype or family history, there is high risk of complications.[1,2,5,8] In patients who are asymptomatic, such as those identified by neonatal screening or because of diagnosis in another family member, treatment may be deferred in favor of a strategy of regular serial observation ("watchful waiting").[2,4,9] If possible, patients should be seen by a specialist or practitioner experienced in caring for GD patients whose best clinical judgment should be used when deciding whether and when to start treatment in these patients. The single most important clinical goal is to prevent development of irreversible disease complications.[2,5,8]

Two classes of disease-specific medications are currently available for the treatment of GD: Enzyme replacement therapy (ERT) and substrate synthesis inhibition therapy (SSIT). Patients may also require adjunctive treatments—medications or surgery—for palliative management of disease manifestations, such as chronic pain and functional joint impairment.[5] ERT is the gold standard of treatment and has been shown to reverse multiple disease manifestations.[2,5,10,11] Only one SSIT, miglustat (Zavesca®), is currently commercially available in the United States. Miglustat is a daily, orally administered medication but is restricted by label to use in adult Type 1 patients who are unable or unwilling to receive ERT.[1,12] Miglustat is usually an effective treatment for GD-associated anemia, thrombocytopenia, and hepatosplenomegaly, but the time frame to achieve a comparable response may be longer than with ERT. Miglustat use is commonly accompanied by gastrointestinal adverse reactions (diarrhea, bloating, weight loss) and sometimes complicated by peripheral neuropathy that is usually, but not invariably, reversible with cessation of miglustat treatment.[2,12]

Table 1 **Enzyme Replacement Therapies[13-15,31]**

	Imiglucerase for injection (Cerezyme®)	Velaglucerase alfa for injection (VPRIV™)	Taliglucerase alfa for injection (Elelyso™)
FDA Approval	1994	2010	2012
Manufacturer	Genzyme	Shire	Pfizer
Indication	Long-term enzyme replacement therapy for patients with confirmed Type 1 Gaucher disease		
Mechanism of Action	Macrophage-targeted enzyme therapy: viscera, especially liver, spleen, bone marrow, and hematological system		
Pediatric Indication?	Yes	Yes	Not yet
Administration	1-2 hour IV infusion	1 hour IV infusion	1-2 hour IV infusion
Label-Recommended Dosing	60u/kg every 2 weeks	60u/kg every 2 weeks	60u/kg every 2 weeks
Source	Chinese hamster cells	Human fibrosarcoma cells	Carrot cells
How Supplied	200 unit vials 400 unit vials	400 unit vials	200 unit vials
AWP	$951.60/200 unit vial $1,903.20/400 unit vial	$1,620.00/vial	$714.00/vial
WAC	$793.00/200 unit vial $1,586.00/400 unit vial	$1,350.00/vial	$595.00/vial

Enzyme Replacement Therapies

Three products are currently available in the United States.[1] Imiglucerase (Cerezyme®) is indicated for long-term therapy of adults and children with Type 1 GD if associated with anemia, thrombocytopenia, bone disease, and/or hepatomegaly/splenomegaly.[13] Imiglucerase has been commercially available since 1994 (the oldest of the three products), and was the only ERT in standard clinical use until the approval of velaglucerase alfa (VPRIV™) in 2010 and taliglucerase alfa (Elelyso™) in 2012.[2,5,13,14,15] In addition to objective clinical benefit, ERTs have been shown to improve patient quality of life and have a positive impact on home and social situations.[5-7]

All three products are recombinant glycoproteins with a similar biochemical structure and are packaged as lyophilized, refrigerated powders requiring reconstitution prior to use. The manufacturing process of these agents is a key differentiating factor.[13-15] Imiglucerase and velaglucerase are produced from cultured mammalian cell lines, whereas taliglucerase is produced from cultured carrot cells.[1,13-15] The clinical significance of this distinction is uncertain, but theoretically, the plant cell cultures should be resistant to animal viral contamination during the manufacturing processes, a problem that did temporarily affect and limit imiglucerase production in recent years.[12,15,16]

Although uncommon, antibody development to ERT that may increase the likelihood of infusion-associated adverse events is possible.[1,2] Most imiglucerase antibodies are non-neutralizing and do not appear to impact the effectiveness of treatment.[17] In some antibody-positive patients, tolerance may develop over time.[1,2] Although standardized antibody test procedures for all ERT products are not yet routine and the published antibody experience with velaglucerase and taliglucerase is still limited by small patient numbers, individuals treated with velaglucerase appear to be less likely to develop ERT-associated antibodies than those treated with imiglucerase or taliglucerase.[1,11,18] Antibodies to one ERT preparation may cross-react with the other ERT products.

Although the recommended dose range for each of these products is the same, treatment should be individualized and initial dosing should be based upon patient symptoms and severity.[1,2,13-15] Clinical improvements, such as normalized laboratory values and resolution of hepatomegaly or splenomegaly, usually occur within the first few years of treatment.[1,2] Because ERT does not cross the blood-brain barrier, it is not effective for definitive treatment or palliation of neuronopathic manifestations in Type 2 and 3 patients. However, ERT should be considered on a selective basis in patients with Type 3 disease as it may help with the non-neuronopathic systemic manifestations that may be key debilitating factors in such individuals.[2,4] In all instances, patients and caregivers should be actively involved in the treatment process and work with experienced specialists to set and define reasonable goals for therapy.[1]

Dosing Changes

Treatment interruptions in symptomatic patients should be avoided due to the risk of disease complications.[2,4,5] However, dosing reductions may be considered in patients in whom treatment is started at higher doses (>45 units/kg body weight every other week) when all relevant clinical goals have been achieved.[1,2,4] Dosing reductions can be accomplished by lowering either the dose itself or, alternatively, the frequency of infusions.[2] However, it is important to bear in mind that GD is a chronic disease and patients will require lifelong treatment in order to maintain the clinical gains achieved with treatment.[2,19]

Product Switch

The three ERTs appear to have comparable safety, efficacy, and dosing profiles (Table 1, page 17).[1,10,11,13-15] This observation creates a possible option to convert patients from one product to another. Clinical studies show that switching between products at a dosing ratio of 1:1:1 is well tolerated with maintenance of disease control.[11,20,21] Switching patients is rarely indicated purely from a clinical viewpoint. However, the importance of the ability to switch between ERT products was patently evident during the imiglucerase drug shortage of 2009-2011.[16]

Treatment Costs

Treatment with ERT is very expensive, with typical costs for the drugs alone, exclusive of infusion fees, in a range of $150,000-$350,000 annually for adult patients.[2,8] At the time of this writing, imiglucerase is the most expensive and taliglucerase the least costly (Table 1, page 17).[19] Currently, Medicare, Medicaid, and most American private insurance plans (traditional and managed care) cover these medications, usually subject to prior authorizations and applicable deductibles so that some patients are subject to major copayment expenses. Despite anticipated changes with the Affordable Care Act, patients continue to fear that they may inevitably consume their lifetime coverage benefits and

> **"By acting as a well-intentioned liaison between the patient and practitioner, payors can create a more structured care coordination process that can help improve outcomes while containing costs."**

personal and family savings.[6,8,19,22] The cost burden can influence many aspects of patient life, including work, travel, and living situation.[6] Fortunately, each ERT manufacturer provides patient assistance programs, with case managers to help with insurance claims and financial assistance (federal, state, or charitable, including manufacturer-funded programs) for patients who are underinsured or uninsured.[23-25] Individualized treatment dosing can help contain these costs while maintaining patient response.[1,26] Additionally, as the products have similar safety and efficacy profiles, product selection, especially in treatment-naïve patients, should include a cost evaluation.[11,21]

ERT administration in hospitals adds significantly to the cost of treatment.[26] Lower cost options, such as home administration or outpatient clinics, are increasingly available and have been shown to be successful.[1,10,21,26] Home administration can save approximately 90 percent of the costs (excluding medication) associated with hospital administration.[6,26] In patients who are able to infuse at home, an improvement has been observed in both work and home life.[2,4,26] Home infusion has also been associated with increased compliance and improved quality of life in patients with GD.[4,5,26] Patients may even be able to self-infuse.[2,26] Insurers, who are appropriately interested in containing healthcare expenses while maintaining optimal patient care, should consider site-of-care management strategies as an important mechanism to reduce the burden of resource utilization in this rare disease population.

Patient Monitoring

Patients should have regular follow-up visits with their treating practitioners and, if possible, periodic evaluations at regional Gaucher disease Centers of Excellence to monitor for disease progression and treatment response.[2,4,27] Clinical response should help guide the frequency of required monitoring.[4,27] Radiographic evaluations should be performed at least every two years, with physical examinations and review of interval history sometimes as often as every six months, especially in children.[2,4,27] Laboratory assessments should be performed every 12 months in untreated patients and every three to six months in patients on ERT.[2] Quality-of-life assessments should also be performed every 12 months in untreated and every one to two years in treated patients.[2] Additionally, all assessments should be repeated at the time of any dose change.[2]

Strategies for Managed Care

Third-party payors can help educate practitioners on the importance of proper medication reconstitution, storage, and handling requirements.[2] Practitioner education should also include the importance of regular disease monitoring and patient follow-up to guide treatment and future monitoring schedules.[2] Payors can assist patients and practitioners with site-of-care issues. Assistance in finding practitioners or treatment sites experienced in GD case management will help patients obtain proper care in as timely a manner as possible and will also help to contain the cost-burden associated with disease complications.[2] In assisting with site-of-care issues, payors may be able to direct patients to lower-cost facilities, such as outpatient infusion clinics, or help them transition to home administration. Payors can also interact with clinics or home infusion companies to identify potential issues and relay information to the treating practitioners to help optimize patient care. By acting as well-intentioned liaisons between patients and practitioners, payors can create a more structured care coordination process that can help improve outcomes while containing costs. They can also promote

and abet patient and caregiver education, emphasizing proper administration techniques as well as recognition of adverse events and the importance of communication and regular follow-up with the treating physicians.[2,26]

Many managed care organizations already have guidance instructions in place for GD ERT.[19,22] Payors should use these in conjunction with expert medical consultants to help ensure proper patient selection, especially for treatment-naïve patients. Among other issues, this might be an opportunity to discuss the possibility of starting new patients on a lower-cost product. In addition, payors can review appropriate patient dosing and regular monitoring results, which will help to contain costs and possibly improve clinical outcomes.

Looking Ahead

A new SSIT, eliglustat, is currently in development.[1,28,29] Study data have shown significant clinical improvement in many key disease parameters.[1,4,29] Additionally, eliglustat appears to be well-tolerated with what to date appears to be a generally acceptable side effect profile.[29] A phase 3 clinical trial is nearing completion. Should success in meeting the trial end points for safety and efficacy lead to regulatory approval, this novel, orally-active agent would provide an additional treatment option for patients, possibly at a lower cost than ERT. The concept of using SSIT and ERT concomitantly is also being explored.[28]

In addition, several investigational compounds belonging to a new class of medications are being studied in GD.[2,30] These low molecular weight compounds are pharmacological chaperones that bind to the enzyme and result in enhanced trafficking of mutant glucocerebrosidases to the lysosome and increased enzyme activity.[2,30] Two potential oral agents—AT3375 and AT2101—are being studied alone and in preclinical trials in combination with ERT.[30]

Editorial support provided by Daria I. Grisanzio, PharmD

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VPRIV® (velaglucerase alfa for injection) **Rx Only**

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
VPRIV is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease.

DOSAGE AND ADMINISTRATION
The recommended dose is 60 Units/kg administered every other week as a 60-minute intravenous infusion.

Patients currently being treated with imiglucerase for type 1 Gaucher disease may be switched to VPRIV. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose when they switch from imiglucerase to VPRIV.

Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Clinical studies have evaluated doses ranging from 15 Units/kg to 60 Units/kg every other week.

VPRIV should be administered under the supervision of a healthcare professional.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions have been reported in patients in clinical studies with VPRIV [see 6, ADVERSE REACTIONS, in full Prescribing Information]. As with any intravenous protein product, hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when VPRIV is administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed.

Treatment with VPRIV should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the active ingredient or excipients in the drug product or to other enzyme replacement therapy.

Infusion-related Reactions
Infusion-related reactions were the most commonly observed adverse reactions in patients treated with VPRIV in clinical studies. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia. Generally the infusion-related reactions were mild and, in treatment-naïve patients, onset occurred mostly during the first 6 months of treatment and tended to occur less frequently with time.

The management of infusion-related reactions should be based on the severity of the reaction, e.g. slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of VPRIV during clinical studies.

ADVERSE REACTIONS
Clinical Studies Experience [see 6, ADVERSE REACTIONS, in full Prescribing Information]
The data described below reflect exposure of 94 patients with type 1 Gaucher disease who received VPRIV at doses ranging from 15 Units/kg to 60 Units/kg every other week in 5 clinical studies. Fifty-four (54) patients were naïve to ERT and received VPRIV for 9 months and 40 patients switched from imiglucerase to VPRIV treatment and received VPRIV for 12 months [see 14, CLINICAL STUDIES, in full Prescribing Information]. Patients were between 4 and 71 years old at time of first treatment with VPRIV, and included 46 male and 48 female patients.

The most serious adverse reactions in patients treated with VPRIV were hypersensitivity reactions [see 5, WARNINGS AND PRECAUTIONS, in full Prescribing Information].

The most commonly reported adverse reactions (occurring in ≥10% of patients) that were considered related to VPRIV are shown in Table 2. The most common adverse reactions were infusion-related reactions.

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.

Table 2 [see 6, ADVERSE REACTIONS, in full Prescribing Information]**:** Adverse Reactions Observed in ≥10% of Patients with Type 1 Gaucher Disease Treated with VPRIV [Naïve to ERT (N = 54), Switched from imiglucerase to VPRIV (N = 40)] Number of Patients (%)—Nervous system disorders: Headache 19 (35.2%), 12 (30%), Dizziness 12 (22.2%), 3 (7.5%); Gastrointestinal disorders: Abdominal pain 10 (18.5%), 6 (15%), Nausea 3 (5.6%), 4 (10%); Musculoskeletal and connective tissue disorders: Back pain 9 (16.7%), 7 (17.5%), Joint pain (knee) 8 (14.8%), 3 (7.5%); Infections and infestations: Upper respiratory tract infection 17 (31.5%), 12 (30%); Investigations: Activated partial thromboplastin time prolonged 6 (11.1%), 2 (5%); General disorders and administration site conditions: Infusion-related reaction* 28 (51.9%), 9 (22.5%), Pyrexia 12 (22.2%), 5 (12.5%), Asthenia/Fatigue 7 (13%), 5 (12.5%).
*Denotes any event considered related to and occurring within up to 24 hours of VPRIV infusion.

Less common adverse reactions affecting more than one patient (>3% in the treatment-naïve group and >2% in the patients switched from imiglucerase to VPRIV treatment) were bone pain, tachycardia, rash, urticaria, flushing, hypertension, and hypotension.

Pediatric Patients
All adult adverse reactions to VPRIV are considered relevant to pediatric patients (ages 4 to 17 years). Adverse reactions more commonly seen in pediatric patients compared to adult patients include (>10% difference): upper respiratory tract infection, rash, aPTT prolonged, and pyrexia.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. In clinical studies, 1 of 54 treatment-naïve patients treated with VPRIV developed IgG class antibodies to VPRIV. In this patient, the antibodies were determined to be neutralizing in an in vitro assay. No infusion-related reactions were reported for this patient. It is unknown if the presence of IgG antibodies to VPRIV is associated with a higher risk of infusion reactions. Patients with an immune response to other enzyme replacement therapies who are switching to VPRIV should continue to be monitored for antibodies.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VPRIV with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS
No drug-drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS
Pregnancy: *Pregnancy Category B.*
Reproduction studies with velaglucerase alfa have been performed in pregnant rats at intravenous doses up to 17 mg/kg/day (102 mg/m^2/day, about 1.8 times the recommended human dose of 60 Units/kg/day or 1.5 mg/kg/day or 55.5 mg/m^2/day based on the body surface area). Reproduction studies have been performed in pregnant rabbits at intravenous doses up to 20 mg/kg/day (240 mg/m^2/day, about 4.3 times the recommended human dose of 60 Units/kg/day based on the body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to velaglucerase alfa.

A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at doses up to 17 mg/kg (102 mg/m^2/day, about 1.8 times the recommended human dose of 60 Units/kg/day based on the body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VPRIV should be used during pregnancy only if clearly needed.

Nursing Mothers: There are no data from studies in lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VPRIV is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of VPRIV have been established in patients between 4 and 17 years of age. Use of VPRIV in this age group is supported by evidence from adequate and well-controlled studies of VPRIV in adults and pediatric [20 of 94 (21%)] patients. The safety and efficacy profiles were similar between pediatric and adult patients [see 6, ADVERSE REACTIONS, and 14, CLINICAL STUDIES, in full Prescribing Information]. The safety of VPRIV has not been established in pediatric patients younger than 4 years of age.

Geriatric Use: During clinical studies 4 patients aged 65 or older were treated with VPRIV. Clinical studies of VPRIV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be approached cautiously, considering potential comorbid conditions.

OVERDOSAGE
There is no experience with overdose of VPRIV.

VPRIV is manufactured by:

Shire Human Genetic Therapies, Inc.
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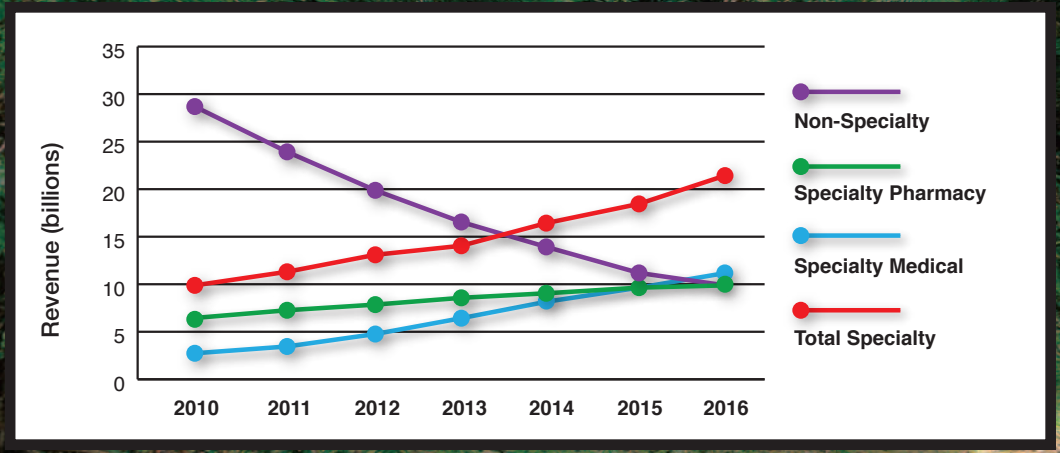


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Appropriate Management of Hereditary Angioedema Within Managed Care

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Hereditary angioedema (HAE) is an uncommon autosomal dominant swelling disorder, usually resulting from an underlying genetic mutation in the C1 inhibitor gene. Two types of C1 inhibitor gene defects have been classified.[1-3] Type I hereditary angioedema, or C1 inhibitor deficiency, is a result of a mutation in one of the two C1 inhibitor alleles that leads to half of the normal output of C1 inhibitor protein. This results in a depressed plasma level of C1 inhibitor protein that is not sufficient to prevent someone from having hereditary angioedema attacks.[1-3] Type II hereditary angioedema is usually associated with normal levels of the C1 inhibitor protein, but in this case, one of the two gene alleles present in patients is abnormal and has a mutation such that half the protein is not functional.[1-3] Thus, both types I and II hereditary angioedema are due to insufficient levels of blood C1 inhibitor protein and both are associated with attacks of angioedema.[1-3]

In recent years, a type III hereditary angioedema has been described. Like types I and II, this appears to be an autosomal dominant disease that can affect both males and females and does not skip generations.[1,3] Both types I and II hereditary angioedema have a predominant clinical expression in females, and this is even more apparent in type III hereditary angioedema.[3,5] However, this disease is not due to C1 inhibitor deficiency. In these patients, C1 inhibitor levels are normal and the level of the protein C4, which is controlled by normal C1 inhibitor levels, is also normal.[1,3,5] At this point, the cause of type III hereditary angioedema is unknown, although the clinical symptoms are similar to those of types I and II.[1,3] A small proportion of patients with type III hereditary angioedema has a defect in clotting factor XII, which may contribute to the onset of attacks. However, most patients do not have this defect.[1,3]

It is certain in types I and II hereditary angioedema that the swelling disorder is due to unregulated and excessive bradykinin release. The triggering of bradykinin receptors on endothelial cells leads to capillary fluid leakage and swelling. The cause of type III hereditary angioedema may be similar, but extensive studies of type III are not yet available.[1,3] Attacks of types I and II hereditary angioedema generally begin in childhood but become markedly more severe following puberty.[1-5] Type III hereditary angioedema has less of a propensity to start in childhood.[1,3]

Table 1 HAE-Specific Medications

Treatment	Indication	Approval	Cost	Route
C1-INH Replacement				
C1 esterase inhibitor [human] (Berinert®)[8]	Acute attacks in adolescents and adults	2009	Approx $6,000/attack	IV HCP or self-admin
C1 esterase inhibitor [human] (Cinryze®)[9]	Prophylaxis in adolescents and adults	2008	Approx $32,000-$45,000/month	IV
Bradykinin Receptor Antagonist				
Icatibant (Firazyr®)[10]	Acute attacks in ≥ 18 years old	2011	Approx $7,000/attack	SC self-injection
Plasma Kallikrein Inhibitor				
Ecallantide (Kalbitor®)[11]	Acute attacks in ≥ 16 years old	2009	Approx $9,000/attack	SC **Black box warning:** Must be administered by HCP with emergency therapy available
Recombinant C1-INH				
Conestat alfa (Rhucin®)[12]	N/A	In late-stage development	N/A	IV

Key: C1-INH=C1 esterase inhibitor; HAE=hereditary angioedema; HCP=healthcare practitioner; IV=intravenous; N/A=not applicable; SC=subcutaneous

Hereditary angioedema is strikingly variable from patient to patient. Even patients in the same family, who have presumably the same genetic defect, may experience varying rates and severity of attacks. Additionally, attacks can affect almost any part of the body. Some patients have attacks mostly limited to their hands, feet, and genital regions, while others have attacks mostly of severe abdominal pain.[1-6] About half of patients have attacks that affect their airways at some time in their lives.[2] In the days before prophylactic or acute treatment was available, the incidence of death from these hereditary angioedema attacks affecting patients' airways approached 30 percent.

Presentation

As mentioned, wide variability exists in the presentation of hereditary angioedema. Some patients have no warning of an attack. Some patients may experience a prodromal phase several hours before an attack starts, while others have erythema marginatum, a red rash that often appears prior to attacks.[1-3,5-6] These symptoms are frequently followed by swelling, which can progress over about 36 hours and then slowly resolve over another 36 hours. Virtually every mucosal surface can be affected by angioedema, but organs such as the brain, heart, lungs, and spleen are almost never affected. In general, the GI tract mucosa, the skin, genital region, and mucosal surfaces are frequently the areas that swell.[1-7] Most patients do not know what brings on an attack but known triggers include medications, particularly estrogen-containing oral contraceptives or hormonal replacement therapy and angiotensin converting enzyme inhibitors.[1,3-5] The latter medication inhibits the breakdown of bradykinin, therefore contributing to an extensive attack.[3] Stress, infections, and local trauma, such as dental surgery, can also bring on attacks, and some patients have a marked propensity to have their attacks during menstruation.[1,3-5]

Diagnosis

Diagnosis is often delayed in patients with hereditary angioedema, sometimes as long as 10 or 20 years. This is primarily due to the rarity of the disease, which may be outside the experience of many general practitioners.[2,5] The actual prevalence of this disease is not known, but estimates have varied from 1 in 10,000 to 1 in 50,000 people.[1-5] The disease should be considered in all patients who have episodic angioedema, or attacks of deep-seated swelling not associated with urticaria or allergy and that do not respond well to antihistamines, epinephrine, or glucocorticoids.[1-6] Correct diagnosis of types I and II hereditary angioedema requires laboratory testing to identify decreased levels or reduced function of the C1 inhibitor protein, depending on the type, as well as decreased complement factor C4.[1,3-5] There still is no clear method for diagnosing type III hereditary angioedema, which presents a difficulty even for experts in the treatment of this disease.[3]

Treatment

Therapeutic management of hereditary angioedema is customarily divided into treatment of acute attacks, short-term prophylaxis (administered in the expectation of a potential swelling event), and long-term prophylaxis.[1-4,7]

Hereditary angioedema attacks do not generally respond to the usual treatment for allergic angioedema, including antihistamines, epinephrine, or glucocorticoids.[1-3] Pharmacologic options for the treatment of acute attacks have become available only in the past few years.[8-12] Before this time, prophylactic agents were available.[1,2,4,7] Two antifibrinolytics, epsilon aminocaproic acid (EACA) and tranexamic acid, were introduced in the late 1960s and 1970s and were shown to be effective in small double-blind studies.[5,7] However, despite prophylactic treatment, patients still have occasional attacks. The mechanism of action of the antifibrinolytics is still not completely known, but it is thought that by inhibiting fibrinolysis, these products down-regulate one activator of the bradykinin pathway that leads to angioedema. EACA became the generally used antifibrinolytic agent in America, but the less toxic tranexamic acid became the preferred agent in Europe. In recent months, tranexamic acid has again become available for oral administration in America. Considerable information about the toxicity of EACA exists, with long-term toxicity including severe muscle toxicity, as well as marked feelings of fatigue. There are no long-term studies of the toxicity of tranexamic acid. In theory, treatment with these agents at the time of thrombosis, such as during a myocardial infarct, would be contraindicated.

In the 1970s, androgens were introduced for the treatment of hereditary angioedema. Taken orally, these drugs are effective in the majority of patients but have a long list of complications that impede their use in many patients. Moreover, they are not effective in some patients, cannot be used in children as they may cause growth abnormalities, and cannot be used in pregnant women or women who want to become pregnant because of possible fetal abnormalities.[1] Danazol (Danocrine®), the first drug generally available following careful double-blind studies, was approved by the FDA and has become the dominant drug used in the treatment of hereditary angioedema in the United States.[1,5,13-14] Stanazolol (Winstrol®), introduced shortly after, is also FDA approved and is approved for use in children. These drugs are not effective in acute attacks and therefore are only approved for prophylaxis. In situations where an angioedema attack might be anticipated, these products can be used as short-term prophylaxis, as well.[1,5] Such situations include dental surgery, automobile accidents, and other kinds of surgery.[1,5]

Fresh frozen plasma was introduced early for the treatment of acute attacks and is effective in the vast majority of patients, supplying the missing C1 inhibitor protein.[1-4] It has become clear over the years that, in a minority of patients, attacks become worse because the same fresh frozen plasma is providing substrate for a generation of bradykinin, which is the mediator of the angioedema. Nevertheless, fresh frozen plasma has been used effectively for short-term prophylaxis, as it does not carry the danger of increased angioedema in patients who are not having attacks at the time of infusion. It has also been used successfully before surgery in a variety of settings.

In 2008, the FDA approved Cinryze®, a plasma-derived C1 inhibitor protein preparation, for the prophylactic treatment of hereditary angioedema, with 1,000 units of nano-filtered C1 inhibitor given intravenously twice a week to patients with fairly frequent attacks.[9] The approval followed decades of use of this drug in Europe and confirms the impression that the Europeans have found this drug to be quite effective. In the following year, another plasma derived C1 inhibitor product, Berinert®, was FDA approved for the treatment of acute attacks. This preparation, at 20 units/kg, terminates attacks in the majority of patients.[8]

Drugs that interfere with either the generation of bradykinin (ecallantide [Kalbitor®]) or the interaction of bradykinin with its receptor (icatibant [Firazyr®]) have also been shown to be effective in acute attacks.[1-5,7,10,11] Ecallantide and icatibant can both be used subcutaneously but are not useful in prophylaxis because of their short half-life.[2,10,11] More recently, recombinant C1 inhibitor has been made available in Europe but is not yet approved for use in the United States.

Burden of Disease

Episodes of swelling and pain associated with the disease often result in disability, discomfort, and markedly decreased quality of life.[5,15] Many patients suffer from the psychological impacts of this disease, particularly depression.[15,16] This may be expected in patients who have seen multiple members of their family with this disease die of asphyxiation. Swelling of the extremities and joints may impede the patient's ability to walk, use a computer, perform the activities of daily living, attend school or work, and take part in social activities.[5,15] Abdominal attacks are particularly devastating and can cause severe pain, leading many of these patients to undergo unnecessary abdominal surgery.[5,17] Attacks lead to frequent

visits to physician's offices, clinics, emergency departments, and hospitals. Patients with very frequent attacks, who comprise up to 20 percent of the hereditary angioedema patient population, have a particularly difficult time with their lives.[15] The frequency of attacks is often dependent upon stress factors, with patients under psychological stress experiencing a greater number of episodes.[5,13]

One report suggests that the total annual medical cost, including both direct and indirect costs per patient, averages almost $42,000 in 2007 U.S. dollars. Total costs associated with severe attacks are much higher due to many visits to the emergency room and hospital admissions. Numbers quoted include $96,000 total and $65,400 spent on emergency room visits alone.[16] Although the costs per patient and per visit are still being defined, some have estimated a direct medical cost associated with acute attacks averages $21,339 per year and makes up 82.4 percent of the total per patient direct medical cost. The largest component of these direct costs is hospital admissions for acute attacks, at an average cost per patient of $17,335, with emergency room visits following at $2,600.

These patients also consume an abundance of outpatient healthcare resources. At least half of the patients see a specialist because the disease is rare, and many primary care physicians are uncomfortable making important medical decisions for these patients with possible life-threatening attacks. Medication expenses for these patients are often costly as well. The low average of $2,000 per patient annually probably reflects the patients who have both mild disease and are taking androgens rather than those who have severe disease and are taking the newer medications.[16]

Misdiagnosis also represents a financial concern in this patient population. Many of these patients present to emergency rooms repeatedly before receiving the appropriate diagnosis, which is not accounted for in the cost estimates.[16]

It has been suggested that hereditary angioedema patients incur indirect costs as well, averaging more than $16,000 in lost wages, decreased productivity, child-care costs, and travel costs per patient annually. The patients with severe disease often find it impossible to locate full-time employment because of missed work due to attacks.[16]

Payor Practices

Payors can improve the management of hereditary angioedema through education, both of the patients and their treating practitioners. Patient education includes proper self-administration methods if the drug is approved for self-administration.[7,15,18,19] Such drugs include the C1 inhibitor preparations and Firazyr®.[8-10] It has been shown that patients are far more responsive to treatment of acute attacks if the attack is treated early. Since all the drugs prevent angioedema formation and do not influence the rate of edema clearance from tissue, attacks that are treated early can be controlled far more rapidly than attacks treated following the development of angioedema. Thus, treating attacks early decreases the costs associated with hospital and emergency room admissions.[15] Because attacks are shortened, self-administration improves the quality of life in these patients.[15] Obviously, for this to be effective, the patients require on-hand medication for self-administration.[7,19]

The importance of seeking emergency hospital care in cases of persistent, severe, or worsening laryngeal symptoms must be stressed. This is a life-threatening condition and should be treated in the emergency room without delay.[1,7,15,19] Patients should be educated on the importance of seeing a practitioner who is familiar with hereditary angioedema. This helps with both disease control and disease cost.[7,19] Experience has shown that education should focus on helping the patient identify and avoid triggering factors, if these can be identified.[1,19] Those who treat hereditary angioedema feel it is essential to instruct patients to keep a diary detailing each attack, including location, duration, severity, precipitating factors, and treatment received, as well as any potential adverse effects of treatment. This helps the physician understand the patient's disease and design the most appropriate therapy.[15,19] Wallet cards or emergency care identification, including diagnosis and necessary treatments, should be provided for patients in case of emergency during acute attacks to help ensure fast and accurate treatment.[1,19] Each patient should have a written treatment plan.

Practitioner education should highlight the importance of early and accurate diagnosis to minimize unnecessary surgeries and tests, particularly in patients presenting with acute, severe abdominal pain.[5,7,17] Early diagnosis helps diminish morbidity and mortality associated with the disease.[5] Education should cover treatment options and any specific requirements, such as the need for available medical support when providing ecallantide (Kalbitor®) due to the minor (but FDA emphasized) risk of anaphylaxis.[7,11]

Payors should stress the importance of patients having a practitioner familiar with hereditary angioedema who will work closely with them to manage and individualize treatment. As such, it is frequently necessary that the patient be followed by a specialist who has particular expertise in the treatment of hereditary angioedema.[5,7] Even when the disease

is under control, practitioners should be encouraged to see patients regularly, at least on a yearly or biyearly basis, to follow the course of the disease, discuss health-related quality-of-life issues, and possibly make medication adjustments.[5,7,19]

Payors have attempted to manage the high cost of hereditary angioedema medications by restricting usage, as in requiring specialty drug benefit coverage, prior authorization, and quantity limitation.[20,21,22] The striking variability between patients and frequency of attacks, severity of attacks, and most frequent site of angioedema make these approaches difficult to manage.[1-7,15] It is clear that treating attacks early is of great benefit to patients, and often patients have prodromal symptoms that tell them they are likely to have an attack.[1-3,5,6] The issue that patients face is that not every prodrome is followed by an attack, and a patient cannot tell how severe an attack is going to be at the start of the attack.[1] Thus, the problem of limiting the number of treatments, as well as requiring prior authorizations, becomes exceedingly difficult. These factors, in addition to extensive patient out-of-pocket costs, have led most manufacturers to offer patient-assistance services, which provide help for treatment-access issues, including determining insurance coverage, covering financial assistance, or paying for copays.[23-26] Payors may also be able to work with pharmaceutical companies to negotiate better pricing.[23]

Intravenous administration in a clinic or physician's office may reduce medication usage versus home-based self-administration.[8-11,15] However, home-based treatment may provide the quickest treatment approach leading to reduced costs associated with hospital admissions and negative outcomes. The use of attenuated androgens approved for hereditary angioedema may assist payors with cost containment and provide a readily assessable treatment option for patients. However, these older agents are associated with side effects, are not useful in some groups of patients, are not effective in acute treatment, and have not been studied in combination with the newer agents.[1,5,13-14,27] All these studies will be required in the future.

Implementing programs to help monitor the disease status of HAE patients is another practice that payors can use. Ensuring that the patients are seen in comprehensive care clinics may assist not only with the care of these patients but also with the monitoring of treatment and the assurance of better treatment outcomes. By working closely with patients and practitioners, payors can help promote early and accurate diagnosis and streamline treatments for patients with hereditary angioedema. Patient and practitioner education is a key component to this plan and should be the primary mechanism for HAE-specific management strategies.

Editorial support provided by Daria I. Grisanzio, PharmD

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Cutting drug acquisition costs for adults with Type 1 Gaucher disease

BY 25%

Now that makes a lot of cents.

In a 1M-member plan, this could save up to $1.64M.[1-3*]

Drug acquisition costs for ELELYSO™ (taliglucerase alfa) are up to 1/4 less than Cerezyme® (imiglucerase for injection) and 12% less than VPRIV® (velaglucerase alfa for injection).[†]

These savings may not reflect the actual cost paid by consumers, pharmacies, or third-party payers. Clinical studies comparing the efficacy and safety of ELELYSO, Cerezyme, and VPRIV in adults with Type 1 Gaucher disease have not been conducted. Approved indications for ERTs are not the same. ELELYSO is indicated for adults with Type 1 Gaucher disease.

[*]Prevalence of Gaucher disease ranges from 1 in 50,000 to 1 in 100,000. Estimated number of eligible patients based on general population prevalence, estimated at 0.0015%.

[†]ELELYSO list price ($595) is at a 25% discount to Cerezyme wholesale acquisition cost (WAC). Cerezyme drug cost ($793) is based on WAC in ReadyPrice® and Medi-Span® databases. Annual costs are calculated based on drug costs for 200 units. Total drug cost reflects the plan's overall financial obligation. Monthly cost is based on number of vials required (includes wastage) and is rounded up (eg, 22.8 vials = 23 vials).

Calculations:
Monthly Cost = Round up (units injected per month/200) x Drug Cost
Annual Cost = Monthly Cost x 12
Annual Savings = Annual Cerezyme Drug Cost – Annual Cost x .75
Average Dose = 30 U/kg and Average Weight = 70 kg

INDICATION

ELELYSO™ (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease.

IMPORTANT SAFETY INFORMATION

As with any intravenous protein product, severe allergic reactions are possible. Anaphylaxis has been observed in patients treated with ELELYSO. If anaphylaxis occurs, ELELYSO should be discontinued immediately, and appropriate medical treatment should be initiated.

In patients who have experienced anaphylaxis during infusion with ELELYSO or with other enzyme replacement therapies (ERTs), caution should be exercised upon retreatment; appropriate medical support should be readily available.

Please see Important Safety Information continued on reverse, and Brief Summary on following page.

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(taliglucerase alfa) for injection
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IMPORTANT SAFETY INFORMATION (continued)

Infusion reactions (including allergic reactions), defined as a reaction occurring within 24 hours of the infusion, were the most commonly observed reactions in patients (44%-46%) treated with ELELYSO in clinical studies. The most commonly observed symptoms of infusion reactions were headache (16%), chest pain or discomfort (6%), asthenia (7%), fatigue (5%), urticaria (7%), erythema (5%), increased blood pressure (5%), back pain and arthralgia (7%), and flushing (6%). Less common infusion or allergic reactions (<2%) included angioedema, wheezing, dyspnea, coughing, cyanosis, and hypotension. Most of these reactions were mild and did not require treatment intervention.

Base the management of allergic or infusion reactions on the type and severity of the reaction, *e.g.*, temporarily stopping the infusion and/or decreasing the infusion rate, and/or treating with medications such as antihistamines and/or antipyretics.

Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely premedicated prior to infusion of ELELYSO during clinical studies.

Other commonly observed adverse reactions in ≥10% of patients were URTI/nasopharyngitis, pharyngitis/throat infection, headache, arthralgia, influenza/flu, UTI/pyelonephritis, back pain, and extremity pain. One patient experienced a type III immune-mediated skin reaction (fixed drug eruption).

As with all therapeutic proteins, patients have developed IgG antidrug antibodies (ADA) to ELELYSO. In a clinical study, 17 of 32 treatment-naïve patients (53%) who were administered ELELYSO developed ADA posttreatment. In a second clinical study, 4 of 28 patients (14%) switched from imiglucerase treatment to ELELYSO treatment developed ADA after the switch. The relevance of ADA to therapeutic response and adverse events is currently unclear.

It is unknown if the presence of ADA to ELELYSO is associated with a higher risk of infusion reactions. Patients who develop infusion or immune reactions with ELELYSO should be monitored for ADA. Additionally, patients with an immune reaction to other ERTs who are switching to ELELYSO should be monitored for ADA to ELELYSO.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELELYSO with the incidence of antibodies to other products may be misleading.

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Please see Brief Summary on adjacent page.

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ELELYSO™ (taliglucerase alfa) for injection **Rx Only**

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE: ELELYSO™ (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Anaphylaxis. As with any intravenous protein product, severe allergic reactions are possible. Anaphylaxis has been reported in patients treated with ELELYSO *[see Adverse Reactions]*. If anaphylaxis occurs, ELELYSO should be immediately discontinued, and appropriate medical treatment should be initiated. In patients who have experienced anaphylaxis during infusion with ELELYSO, caution should be exercised upon rechallenge; appropriate medical support should be readily available *[see Adverse Reactions]*.

Allergic and Infusion Reactions. Infusion reactions (including allergic reactions), defined as a reaction occurring within 24 hours of the infusion, were the most commonly observed reactions in patients (44%-46%) treated with ELELYSO in clinical studies *[see Adverse Reactions]*. The most commonly observed symptoms of infusion reactions were headache (16%), chest pain or discomfort (6%), asthenia (7%), fatigue (5%), urticaria (7%), erythema (5%), increased blood pressure (5%), back pain and arthralgia (7%), and flushing (6%). Other infusion or allergic reactions included angioedema, wheezing, dyspnea, coughing, cyanosis, and hypotension. Most of these reactions were mild and did not require treatment intervention. Base the management of infusion reactions on the type and severity of the reaction, *e.g.*, slowing the infusion rate or treatment with medications such as antihistamines and antipyretics. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of ELELYSO during clinical studies.

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 data described below reflect exposure to ELELYSO in 60 patients ages 13 to 74 years who received ELELYSO at doses ranging from 11 to 73 Units/kg every two weeks in 3 clinical studies, and included 31 males and 29 females. Thirty-two patients were naïve to ERT (Study 1) and 28 were switched from imiglucerase to ELELYSO (Study 2) *[see Clinical Studies]*. Study 3 includes patients continuing treatment from Study 1 and Study 2. Twenty-four patients were treated for longer than 2 years and 4 patients were treated longer than 3 years. One patient experienced a Type III immune-mediated skin reaction. The most common adverse reactions requiring interventions were infusion reactions *[see Warnings and Precautions]*.

Table 2: Adverse Reactions that Occurred in ≥10% of Patients Treated with ELELYSO

	Study 1	Study 2
Preferred Term	**N=32**	**N=28**
Infusion reaction	14 (44%)	13 (46%)
URTI/Nasopharyngitis	7 (22%)	5 (18%)
Pharyngitis/Throat infection	6 (19%)	1 (4%)
Headache	6 (19%)	3 (11%)
Arthralgia	4 (13%)	3 (11%)
Influenza/Flu	4 (13%)	1 (4%)
UTI/Pyelonephritis	3 (9%)	3 (11%)
Back pain	1 (3%)	3 (11%)
Extremity pain	0	3 (11%)

The types and incidences of adverse reactions with up to 24 months of treatment in study 3 were similar to study 1 and study 2. In addition to those listed in Table 2, less commonly reported adverse reactions (>2%) observed in clinical trials include fatigue, pain, pharyngolaryngeal pain, pruritus, diarrhea, dizziness, nausea, bone pain, abdominal pain, erythema, flushing, edema peripheral, muscle spasms, paresthesia, dyspnea, throat irritation, asthenia, chest discomfort, infusion site pain, alanine aminotransferase increased, musculoskeletal discomfort, musculoskeletal pain, insomnia, rash, and skin irritation.

Immunogenicity. As with all therapeutic proteins, patients have developed IgG anti-drug antibodies (ADA) to ELELYSO. In study 1, seventeen of 32 treatment naïve patients (17/32, 53%) who were administered ELELYSO every two weeks developed ADA post-treatment (defined as ADA positive at one or more post-treatment time points). Two additional patients were antibody positive at baseline; one patient withdrew after developing an allergic reaction with the first dose of ELELYSO and the second patient had increasing antibody titerswith continued treatment. In study 2, four of 28 patients (4/28, 14%) switched from imiglucerase treatment to ELELYSO treatment once every two weeks developed ADA after the switch. One additional patient who switched from imiglucerase in Study 2 was positive at baseline but did not develop increased ADA titers after ELELYSO treatment. The relevance of ADA to therapeutic response and adverse events is currently unclear. Using neutralizing antibody assays of limited sensitivity, two treatment naïve patients (at 24 months of ELELYSO treatment) and one patient switched from imiglucerase (at 9 months of ELELYSO treatment) were determined to be positive for neutralizing activity in an *in vitro* enzyme inhibition assay and were negative in a cell based assay. For these patients there was no demonstrated association between positive neutralizing antibody assay results and therapeutic response. The significance of these findings is unknown at this time. It is unknown if the presence of ADA to taliglucerase alfa is associated with a higher risk of infusion reactions. Patients who develop infusion or immune reactions with ELELYSO treatment should be monitored for ADA to ELELYSO. Additionally, patients with an immune reaction to other enzyme replacement therapies who are switching to ELELYSO should be monitored for ADA to ELELYSO. Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELELYSO with the incidence of antibodies to other products may be misleading.

USE IN SPECIFIC POPULATIONS:

Pregnancy. Category B: Reproduction studies with taliglucerase alfa have been performed in pregnant rats at intravenous doses up to 55 mg/kg/day (about 5 times the recommended human dose of 60 Units/kg based on the body surface area) and in pregnant rabbits at intravenous doses up to 27.8 mg/kg/day (about 5 times the recommended human dose of 60 Units/kg based on the body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to taliglucerase alfa. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ELELYSO should be used during pregnancy only if clearly needed.

Nursing Mothers. There are no data from studies in lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELELYSO is administered to a nursing woman.

Pediatric Use. The safety and effectiveness of ELELYSO in pediatric patients have not been established. One 8 year-old pediatric patient experienced a serious adverse reaction (gastroenteritis).

Geriatric Use. During clinical studies 8 patients aged 65 or older were treated with ELELYSO. Clinical studies of ELELYSO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE: There is no experience with overdosage with ELELYSO.

PATIENT COUNSELING INFORMATION: Administer ELELYSO under the supervision of a healthcare professional. ELELYSO is a treatment that is given intravenously every other week. The infusion typically takes 60 to 120 minutes. Advise patients that ELELYSO may cause hypersensitivity reactions or infusion-related reactions. Infusion-related reactions can usually be managed by slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions. Carefully re-evaluate treatment with ELELYSO in the presence of significant evidence of hypersensitivity to the product *[see Warnings and Precautions]*.

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LAB-0610-1.0

Neurotoxins: Clinical and Financial Implications for Managed Care

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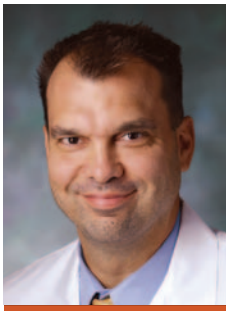

Zoltan Mari, MD

Botulinum toxin, a protein complex neurotoxin, has developed into a class of medication with a growing number of indications and uses.[1,2] In the United States, there are four botulinum neurotoxins (BoNT) currently on-market: Botox® (onabotulinumtoxinA–including separately marketed Botox Cosmetic®), Xeomin® (incobotulinumtoxinA), Dysport® (abobotulinumtoxinA), and Myobloc® (rimabotulinumtoxinB).[3-7] The pharmaceutically manufactured toxins are produced under the anaerobic fermentation of *Clostridium botulinum* and are then purified.[1,3] These injectable medications are all toxin type A (Hall strain), with the exception of Myobloc, which is toxin type B (Bean strain).[3-7] BoNT works via inhibition of acetylcholine release at the synaptic cleft.[3-8] Effects of BoNT include decreased muscle contraction and decreased glandular secretion.[1,8] The approved indications include treatment of cervical dystonia, blepharospasm, glabellar lines, and the newly approved indication of overactive bladder, among others.[3-7]

Type A Versus Type B

While there are seven serotypes of BoNT (types A-G), only two types (A and B) are commercially available for human clinical use.[1] The BoNT structural complex contains the neurotoxin as well as associated proteins, which may protect the structural complex and aid in its absorption.[1,9] Xeomin lacks the accessory proteins that are present in the other BoNT products, a characteristic that may limit the production of neutralizing antibodies, although the clinical benefits of this assumption have not been conclusively proven.[5,9] The different physiological effects of serotypes A and B are due to their differing binding affinities for acetylcholine receptors within different tissues types.[1]

Efficacy between the two serotypes is generally similar.[9,12] Clinical efficacy is usually noted within one week and peak efficacy after two weeks, with a duration lasting two to four months or longer.[1,14-15] Physiologic recovery after injections also appears to be similar between the two serotypes.[12] Repeat treatments are recommended at intervals no less than every three months.[1,3-7] Injections less than every three months are not recommended due, in part, to concerns regarding the development of neutralizing antibodies.[1]

The potency also varies between serotypes, with type A being the most potent and having the longest duration of action.[1,8] Potency is reported in terms of the median lethal dose (i.e., the dose needed to result in the death of 50 percent of the

mouse test population), although potency labeling is unique to each product and not directly comparable.[1] In mice, Botox and Xeomin are relatively comparable in terms of potency and are less potent than Dysport, while Myobloc is significantly more potent than any of the other BoNT products. As BoNT have different relative potency in humans and mice, when referring to potency in humans relative to mice, Botox and Xeomin are the most potent, followed by Dysport, with Myobloc having the lowest potency.[10,11] It should be noted that there currently is no measure that could provide a unified potency analysis and that these mouse lethal dose assays carry a degree of uncontrollable subjectivity. However, when dosed to produce similar efficacy, durations of action are similar among the different serotypes.[12]

Additionally, the diffusion or spread after injection may vary.[12] Type A has been noted to have greater spread into non-injected muscles after administration than type B, when compared at equivalent doses.[8,12] However, type B is noted to have greater systemic spread than type A.[12] This can have implications for the safety of the products and contribute to the differences in adverse event profiles between the two types.[8,12] As a result, type B BoNT use is associated with more frequent autonomic adverse events, even when dosing adjustments are taken into consideration.[12,13]

Neutralizing Antibodies

Neutralizing antibodies (NAB) are antibodies against the neurotoxin component of BoNT.[1,16] NAB development is rare but can occur in up to 18 percent of patients, usually within the first two to three years of treatment.[1,9,16-18] Antibodies are categorized as neutralizing (preventing neurotoxin binding) or non-neutralizing (neurotoxin binding is not affected) and are specific to serotype.[1,9] However, antibodies (both neutralizing and non-neutralizing) reactive against both A and B serotypes have been reported.[1] As a result, patients may become non-responsive to BoNT treatment and potentially to all products in the class.[17] By most experts, this is assumed to occur very rarely. Also, immunity-related resistance is usually self-limited. Clinical implications of NAB development include treatment failure, loss of effectiveness to a class of medications, and the need to seek other forms of treatment, such as surgery.[9,16-17]

NABs may develop due to product factors including formulation and chemical properties. Of particular note, the accessory protein component may contribute to NAB development; as noted previously, Xeomin lacks these proteins and is reported as having little to no NAB development.[1,5,9,16] Dosing (volume per session or cumulatively, increased dosing frequency, long-term treatment) or patient (genetic, immune system, gender, age) factors may also influence NAB development.[1,16,17,19]

Costs of Treatment

Treatment with BoNT can be expensive. In addition to the high cost of the products, treatment with BoNT requires in-office administration and may require the use of specialized equipment, transportation, or nursing assistance.[13,15] Separate facility fees, which are based on the space, services, and supplies/equipment used, may also be assessed if procedures are performed in hospitals.[20,21] When taking into account associated costs, such as transportation or nursing assistance, treating spasticity and rigidity is associated with a 45 to 93 percent increase in costs compared to an increase of only 15 to 37 percent when treating other indications (facial hemispasm, blepharospasm, dystonias, autonomic disorders).[15]

Another factor impacting the cost burden is the effect these disease states have on quality of life and the associated impact on society. One example is in patients with focal dystonias, a disorder characterized by involuntary and invalidating muscle contractions. In cervical dystonia, disabling neck pain has been observed in three-quarters of patients. In addition to the physical symptoms, pain, and disability, nearly half of the patients with cervical dystonia meet the criteria for depression.[13] Prior to treatment with BoNT, only approximately half of these patients were working.[13] BoNT treatment has been demonstrated to relieve dystonic symptoms and significantly reduce pain in these patients.[13] Treatment with BoNT has also been noted to help improve the quality of life of these patients and allow many of them to return to work.[13,22]

The costs of therapy and cost-benefit ratios vary between indications.[15] In some cases, the cost-benefit may be minimal. For example, initiating BoNT every three months for migraine prophylaxis is associated with a less than 1 cent per member per month increase in cost. However, this cost does not take into consideration the financial benefits associated with decreased rates of concomitant medications to manage patient symptoms or disease states.[23] For other indications, such as neurogenic detrusor overactivity, the cost-savings may be greater by using BoNT.[24] In this case, the average reimbursement in 2008-2009 U.S. dollars for BoNT type A treatment was $2,946.83 as compared to $25,041.53 for an augmentation cystoplasty, making BoNT treatment the more cost-effective choice over five years ($28,065 versus $33,272 for cystoplasty).[24]

Product Selection

When selecting which BoNT to use, a number of factors come into consideration, including indication, proven efficacy, and safety. Botox has been available the longest and has the widest range of indications; however, it also carries the highest cost. When treating cervical dystonia, an indication held by all four products, estimated costs for one treatment session

are the most expensive with Botox and the least expensive with Xeomin (Table 1, page 35). The price of each particular product may also vary based on negotiated pricing among the manufacturers and purchasers, such as specialty pharmacies and hospitals. As such, selection of a cost-effective product should be a consideration, especially when the medications have similar efficacy for treating a given condition.[9] Product selection may also be based on potency, especially as it relates to vial size and lower cost per session. Using Dysport when treating large areas, such as lower and upper limbs, for example, may be a cost-effective option.[22,25] Although a single vial of Dysport costs more, each vial contains more units and fewer vials would be needed than if another product, such as Botox, were to be used. This can result in a substantial cost-savings of 10 to 32 percent per patient per injection.[22,25] Botox also has a maximum dosage per three months, which may be exceeded if treating large areas or multiple sites on a patient.[6] Additionally, while efficacy can be augmented by increasing the administered dose, it does so at the cost of increasing adverse events.[11,13]

Several differences among the four products exist that affect the physiological actions of each.[9] In addition to the differences in relative potency and duration of action due to chemical structure and formulation, injection-site factors, such as the type of muscle being treated, may also have an influence on product selection.[2,8-9] Onset of action may also vary among products. Xeomin may have an earlier onset, as was reported in a manufacturer-sponsored study.[9] Diffusion properties of the drug in the tissue, while potentially influencing effect, can be controlled for through administration and dosing techniques.[2,8-9,14] The treating practitioner can influence the efficacy of the medications by varying the drug dilution, volume of drug used, number of injections in the treatment area, and other injection-technique adjustments.[8,12] Duration of action may be modified to a degree by adjusting the amount of medication injected.[8,12]

The adverse event profiles of type A products are relatively similar to one another, but differ compared to type B.[9,14] These differences may impact product selection for specific indications. For example, Myobloc has a greater affinity for salivary glands and can produce more frequent dysphagia and dry mouth.[11,26] In this case, a different product may be preferable when treating conditions such as cervical dystonia.

Depending on the site of care, administration factors may also come into consideration when selecting which product to use. Xeomin is the only product that does not require refrigerated storage. Once reconstituted or opened, the respective manufacturers recommend that Botox and Xeomin be used within 24 hours, while Dysport and Myobloc be used within four hours.[3-7]

A few articles have been published on usage practices or as guidelines for BoNT. However, there are currently no standard guidelines that exist regarding the dilution and preparation of the available products.[12,14,27] These publications address technique, dosing, and any potential hindrances or aids for treatment and may be written for a specific indication or address each treatment area individually.[14,27]

Conversion and Product Interchange

The A and B serotypes are not interchangeable.[1] The individual type A products are also not bioequivalent and therefore not interchangeable.[1,3-8,14] However, conversion among products is still of interest, and debate exists regarding the correct conversion factors, as no standard guidelines are currently available.[8,14] The conversion between Botox and Xeomin appears to be a consistent 1:1 in published literature.[9,16,19] The conversion between Botox and Dysport is believed to be more variable, ranging between 1:2 to 1:4 but with some consensus around 1:3.[8-10,14] Conversion of Botox to Myobloc appears to be closer to 1:40 but may range up to 1:100.[10-12,19]

Switching among products is generally discouraged, as there is little evidence to support this practice.[19] Confounded by the lack of set conversion factors, product interchange could easily lead to significant changes in dose.[28] It may also be difficult to discern whether clinical efficacy after switching among products is due to the new product or merely to the potentially increased dose.[28] This may be especially true if switching to Dysport.[10] However, there may be occasions when clinical benefit can be seen by switching products, which may be done without significant risk of adverse events and while maintaining clinical efficacy.[19] In cases of systemic immune reaction, product interchange from Botox to Xeomin may result in continued clinical response without an adverse reaction.[29] Likewise, in cases of NAB development, switching from another type A product to Xeomin may prove effective, although evidence of this is limited.[16] However, due to NAB specificity to serotype, switching to the type B product may be effective.[1] Switching products in cases of nonresponse or partial response may also result in clinical benefits.[16,19]

Off-Label Usage

All four products are often used off-label. This includes using one product for an indication held by another BoNT product, such as Xeomin in upper limb spasticity.[16] This type of usage would follow logically as the efficacy and adverse event profiles of the various products are similar, as described above. BoNT may be used more frequently in some off-label indications, such as wrinkles or achalasia, than in others.[2] Off-label uses include cranial and ophthalmic disorders (e.g., hemifacial spasm, bruxism, migraine, tension headache, neuralgia, ptosis, rhinitis, lacrimation), focal dystonias (e.g., foot and hand

Table 1

Botulinum Neurotoxin Medications

	OnabotulinumtoxinA (Botox®)[3]	OnabotulinumtoxinA (Botox Cosmetic®)[4]	IncobotulinumtoxinA (Xeomin®)[5]	AbobotulinumtoxinA (Dysport®)[6]	RimabotulinumtoxinB (Myobloc®)[7]
Toxin	Type A	Type A	Type A	Type A	Type B
Indication	Adults with failed prior treatment of overactive bladder Urinary incontinence (neurological condition-associated detrusor overactivity) Adults for chronic migraine prophylaxis Adults with upper limb spasticity Adults with severe axillary hyperhidrosis Blepharospasm with dystonia in ≥12 years Strabismus in ≥12 years	Adults (≤65 years) with moderate/severe glabellar lines	Adults with cervical dystonia Adults with blepharospasm (previously treated with Botox®) Adults with moderate/severe glabellar lines	Adults with cervical dystonia Adults (<65 years) with moderate/severe glabellar lines	Adults with cervical dystonia
Approval	1989	1989	2010	2009	2000
Administration Site	Intramuscular, intradetrusor, intradermal	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Dosing	Overactive bladder: 100 Units Neurological condition-associated detrusor overactivity: 200 Units Chronic migraine: 155 Units Upper limb spasticity: based on presentation and prior (adverse) response Cervical dystonia: based on presentation and prior (adverse) response (lower initial dose if botulinum toxin-naïve) Axillary hyperhidrosis: 50 Units/axilla Blepharospasm: 1.25-2.5 Units into each of 3 sites/affected eye Strabismus: 1.25-2.5 Units Max 360 Units/3 months	20 Units Max 360 Units/3 months	Cervical dystonia: 120 Units Blepharospasm: Same as previous Botox® dose or 1.25-2.5 Units/inj site Glabellar lines: 20 Units every 3+ months	Cervical dystonia: 500 Units then every 12-16+ weeks at 250-1,000 Units Glabellar lines: 50 Units every 3+ months	2,500-5,000 Units (lower initial dose if botulinum toxin-naïve)
How Supplied	Single-use vial 100 Units 200 Units	Single-use vial 50 Units 100 Units	Single-use vial 50 Units 100 Units	Single-use vial 300 Units 500 Units	Single-use vial 2,500 Units/0.5 mL 5,000 Units/1 mL 10,000 Units/2 mL
Reconstitute	Yes	Yes	Yes	Yes	No
Cost[34]	$635/100 Unit vial $1,265/200 Unit vial	$635/100 Unit vial	$260/50 Unit vial $515/100 Unit vial	$857/500 Unit vial	$319.40/2,500 Unit/0.5 mL vial $633.80/5,000 Unit/1 mL vial $5,035.40/8-10,000 Unit/2 mL vials

dystonias, tardive dyskinesia, Tourette's syndrome, tremor), urologic disorders (e.g., urethrism, installation of an artificial bladder, vaginism), and gastroenterology and proctology (e.g., esophageal disorders, anal fissure).[1,2] The use of Botox for lower limb spasticity and Dysport for tension headaches has also been reported.[1]

Payor Practices

Clinical experience is an important factor in the overall safety and treatment efficacy when using BoNT.[12,14] Additionally, dosing schedules and dilutions can vary among practitioners. As such, there may be both patient and payor benefits gained from patients seeing specialists experienced in using BoNT for a particular indication.[1,8,14] Dosing should be individualized to the patient, which will help improve patient safety and benefit while assisting in containing the costs of treatment.[14] Payors can educate practitioners on these points as well as stress the principle of starting low and going slowly with regard to dosing, with patient assessments between visits.[14] Periodic follow-up will allow practitioners to assess

toxicity and efficacy, including whether there is early dose wearing or if the patient is continuing to have clinical benefit, even beyond the typical three-month time frame. Patients with extended clinical benefit may be able to wait longer than three months for injections, potentially decreasing the risk of adverse events and NAB development, and resulting in cost-savings for patients, practitioners, and payors.

Payors should bear in mind the wide variety of indications (both on- and off-label) for which these products are used. Currently, many plans may deny claims for off-label uses; however, by covering claims for off-label uses that have demonstrated efficacy, payors may see cost-savings compared to more expensive treatment options, such as surgery.[17,30-31] Additionally, plan requirements, such as prior authorization, may help plans ensure that patients are being treated appropriately with these medications in both on- and off-label uses.[32] Payors can also use this opportunity to ensure that patients are being seen by practitioners who are properly trained and experienced in the use of BoNT.[1,14]

Payors can also help minimize costs by encouraging practitioners to schedule patients in a way that is most effective, such as scheduling patients who will not need a whole vial of product in consecutive appointments; in this way, the vial may be split, which is not just cost-effective but will also decrease waste.[14,22,30,33] Practitioners should be reminded to bill for the exact dosage of the drug administered, follow aseptic injection practices, and use the product within the appropriate time frame once it has been opened or reconstituted.[14,30,33]

Although BoNT is a complicated medication category, understanding the product nuances, medication selection, and impact on clinical outcomes can help in the development of cost-effective management strategies that can not only contain costs to payors but also improve outcomes for patients suffering from a variety of medical conditions.

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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

AND...

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

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

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

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

Important Safety Information

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

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

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

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

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

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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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Manufactured for and Distributed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation, Inc., San Francisco, CA 94105
Issued: August 2012
12A005-ENZ-BRS
Rx Only

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MEDIVATION

Appropriate Use of Antiplatelet Therapy in Patients with Acute Coronary Syndrome

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Acute coronary syndrome (ACS) refers to a group of cardiovascular conditions associated with the obstruction of coronary arteries, thereby limiting access of oxygenated blood to the heart. The term ACS includes the conditions of unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). It is currently one of the most common cardiovascular illnesses in the United States. In addition to the high prevalence, ACS results in significant morbidity and mortality, with close to 30 percent of patients hospitalized for an ACS-related complication within one year of onset.[1,2] ACS is also associated with a substantial economic burden. It is projected that coronary heart disease (CHD) will result in nearly $47 billion in direct healthcare costs in 2015, of which the majority can be derived from ACS.[3]

A primary mechanism leading to the obstruction of blood to the heart is the activation of platelets and the adhesion of activated platelets to the arterial walls. For this reason, the therapeutic use of aspirin for its antiplatelet effects has been a standard of therapy and should be started as soon as possible in patients with ACS.[4,5,6] In fact, best practice guidelines, including those published by the American College of Chest Physicians (ACCP), recommend the use of dual antiplatelet therapy.[6] Recommended dual antiplatelet therapy consists of low-dose aspirin (≤100 mg/day) in addition to either clopidogrel (Plavix®), prasugrel (Effient®), or ticagrelor (Brilinta®). Ticlopidine (Ticlid®) was the first approved thienopyridine but is now rarely used due to the risk for neutropenia.[6]

Overview of Antiplatelet Therapies

Thienopyridine antiplatelet drugs have been used in ACS for more than 20 years.[7] As previously mentioned, ticlopidine was the first approved thienopyridine but has been largely replaced by clopidogrel, a product demonstrating improved efficacy and better tolerability.[8] Clopidogrel, an oral thienopyridine that irreversibly blocks adenosine diphosphate (ADP) receptor P2Y12, established its efficacy by demonstrating a 20 percent relative risk reduction in a composite end point of death from cardiovas-

cular causes, nonfatal myocardial infarction, or stroke in patients with NSTEMI who received clopidogrel plus aspirin vs. aspirin alone (9.3 percent vs. 11.4 percent; p<0.001).[9]

Although this marked a substantial improvement over aspirin monotherapy in patients with ACS, there are several drawbacks to the use of clopidogrel. Clopidogrel is associated with a delayed onset of action, interindividual variability in platelet response, and irreversibility of platelet inhibition leading to a prolonged offset of action.[10] Following absorption, clopidogrel, a prodrug, requires a two-step biotransformation process to become an active metabolite. This activation includes the cytochrome P-450 (CYP) system.[11] This CYP isoenzyme activity results in drug-drug interactions and is affected by genetic polymorphisms, with approximately 15 to 30 percent of patients reported to be nonresponsive to clopidogrel.[12,13] Patients with a reduced functioning CYP2C19 allele may be resistant to clopidogrel and have an increased risk of recurrent cardiovascular events, thrombotic complications, and complications during angioplasty.[14]

The next thienopyridine approved for use in ACS was prasugrel. Similar to clopidogrel, prasugrel irreversibly inhibits the ADP P2Y12 receptor and is a prodrug. However, after intestinal absorption, it is rapidly hydrolyzed to an intermediate metabolite that then only requires a single CYP-dependent step to generate its active metabolite.[10,15] Unlike clopidogrel, prasugrel has not been shown to be impacted by genetic polymorphisms in CYP isoenzymes.[10,16] This leads to reduced interindividual variability in platelet response compared with clopidogrel. Additionally, prasugrel has been associated with a more rapid onset of action and a greater degree of platelet inhibition compared with clopidogrel.[10,17] In the TRITON-TIMI 38 trial, prasugrel demonstrated a 19 percent relative risk reduction in the primary efficacy end point—a composite of the rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke—compared to clopidogrel (9.9 percent vs. 12.1 percent; p<0.001).[15] However, the follow-up period of this trial demonstrated that there was no difference in overall mortality between the treatment groups and prasugrel was associated with a significant increase in the rate of major bleeding compared with clopidogrel.[10,15] In patients who underwent coronary artery bypass surgery (CABG), prasugrel resulted in a rate of major bleeding exceeding four times the rate of clopidogrel. For this reason, prasugrel contains a boxed warning for patients at a high risk of bleeding, including those greater than 75 years of age, less than 60 kg, and patients with a history of transient ischemic attack or stroke. Additionally, due to the trial design, prasugrel is largely restricted to only patients being managed with percutaneous coronary intervention (PCI) after coronary anatomy has been defined.

The most recent approval of an antiplatelet agent indicated for treatment of ACS is ticagrelor. Ticagrelor is an oral cyclopentyl-triazolo-pyrimidine that directly and reversibly binds to the ADP P2Y12 receptor.[18] Ticagrelor does not require biotransformation for activation and has demonstrated improved pharmacologic characteristics compared with clopidogrel—specifically, a greater inhibition of the targeted receptor that is more rapid and consistent with the additional benefit of having a faster offset should antiplatelet therapy need to be discontinued.[10,19,20] The PLATO trial compared ticagrelor and clopidogrel for the prevention of cardiovascular events in more than 18,000 patients with ACS.[21] The trial compared the products based on the primary end point, a composite of death from vascular causes, myocardial infarction, or stroke at 12 months. Ticagrelor showed a 16 percent relative risk reduction compared with clopidogrel (9.8 percent vs. 11.7 percent; p<0.001).[21] In addition, these benefits were observed without increases in the risk of overall major, life-threatening, or fatal bleeding. However, ticagrelor did demonstrate side effects that were absent in patients treated with clopidogrel, including dyspnea, ventricular pauses, anxiety, and mild elevations in serum creatinine and uric acid. These side effects are thought to be due to the blockage of adenosine reuptake by red blood cells.[10]

A rational concern associated with ticagrelor therapy was derived from a subset analysis of the PLATO trial evaluating the use of ticagrelor in the United States. Less than 8 percent of patients enrolled in this trial were in the United States and the analysis of this group suggested a lack of benefit with ticagrelor compared with clopidogrel. This same trend was not observed when evaluating non-U.S. sites. After completing further analysis, the variable most likely to explain this trend was geographic differences in aspirin dose. More than 53 percent of U.S.-treated patients were maintained on a median aspirin dose of ≥300 mg/day during the course of the trial compared with only 1.7 percent of non-U.S. patients. When evaluating low-dose versus high-dose aspirin patients, some interesting trends were identified. Ticagrelor patients on low-dose aspirin therapy had the

lowest rates of cardiovascular events in the trial. In fact, a trend was present toward superiority with ticagrelor compared with clopidogrel in U.S. patients who received a maintenance aspirin dose of ≤100 mg/day, and in non-U.S. patients this trend was proven to be statistically significant.[10,21] This was an important finding and led to a boxed warning for ticagrelor recommending that patients take a maintenance dose of aspirin not to exceed 100 mg/day.

Onset/Offset of Antiplatelet Therapy

With all antiplatelet therapy, it is important to consider both the onset and offset of action. When a patient presents with ACS, a major therapeutic goal is to achieve a steady state of antiplatelet activity rapidly and consistently while limiting the risk of bleeding. Alternatively, should antiplatelet therapy need to be discontinued, a fast offset is beneficial to limit the risk of bleeding during surgical interventions. To determine whether pharmacodynamic differences exist between ticagrelor and clopidogrel, the ONSET/OFFSET study was conducted in patients with stable coronary artery disease.[13]

This study demonstrated that within one hour of the ticagrelor loading dose, inhibition of platelet aggregation (IPA) was greater (~80 percent) than the maximum IPA achieved after clopidogrel loading (~58 percent), which occurred eight hours after the clopidogrel loading dose. Additionally, there was no difference in IPA 24 hours after the last dose between ticagrelor- and clopidogrel-treated patients.[10,13] This is important, as ticagrelor is dosed twice daily and adherence is often an issue in patients with ACS. These results show that if a ticagrelor patient misses a dose, his or her IPA 24 hours following the last dose will be at least as high as a patient on clopidogrel therapy.[10] This study also showed that the greater antiplatelet effect of ticagrelor was sustained during maintenance therapy and the offset effect for ticagrelor was significantly faster than clopidogrel.[13]

Revisions to Best Practice Guidelines

Following the U.S. approval of ticagrelor, several organizations have revised their ACS best practice guidelines. In 2012, the first major guidelines revised to incorporate ticagrelor were the ACCP guidelines on antithromobotic therapy. The ACCP guidelines now suggest choosing ticagrelor over clopidogrel in ACS patients, based on the results of the PLATO study.[9,22] According to the ACCP, it is suggested that ticagrelor be used first-line for patients in the first year after an ACS event regardless of whether they have undergone PCI.[9]

Columbia University Medical Center/New York-Presbyterian Hospital also updated its Clinical Pathways for ACS and Chest Pain following the approval of ticagrelor.[10] In these pathways, ticagrelor has been added as the first-line agent in all patients with ACS, including both STEMI and NSTEMI. Similar to the ACCP, this decision was primarily based on the robust reduction in all-cause and cardiovascular mortality present with ticagrelor in the PLATO study.[10]

Implications for Managed Care

As health insurance providers are being held more and more accountable for the quality of care provided to their beneficiaries, managed care organizations should be trying to identify strategies to improve outcomes in their members with chronic conditions. With the rates of obesity increasing throughout the country, cardiovascular diseases will remain highly prevalent and a good target for quality improvement initiatives. Ideally, by improving outcomes in these patients, managed care organizations would experience financial benefits associated with reductions in overall healthcare utilization. However, regardless of economic rewards, reducing morbidity and mortality in members with cardiovascular conditions should be a primary concern.

In patients with ACS, medication adherence and persistency remains suboptimal. Patients should be continuing their dual antiplatelet therapy for at least 12 months following an event, but many patients discontinue prematurely, usually within the first six months. This places patients at an increased risk for subsequent attacks, for which payors will be financially responsible. Implementing comprehensive adherence programs, although resource intensive, may provide patients with the support required to complete their duration of therapy and reduce the likelihood of additional hospitalizations.

Another major concern impacting clinical outcomes in patients with ACS is transitions in care. In general, patients get initiated on antiplatelet therapy during a hospital stay. However, once these patients are discharged, a substantial number will be lost to therapy. This may be due to a variety of reasons, but access to prescribed medications may be a major contributor. Each of the three available products has unique characteristics that make it appropriate for certain patients. Interventional cardiologists match these characteristics with various patient-specific variables, such as planned intervention, prior medical history, age, weight, and contraindications.

Table 1 Antiplatelet Therapies in the Treatment of ACS[11,15,18,24]

	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)
Manufacturer	Generically available	Eli Lilly	AstraZeneca
FDA Approval	1997	2009	2011
Class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolo-pyrimidine
Indication	ACS (UA, NSTEMI, and STEMI); Recent MI, recent stroke, or established peripheral arterial disease	Reduction of thrombotic CV events in patients with ACS who are to be managed with PCI	Reduce the rate of thrombotic CV events in patients with ACS (UA, NSTEMI, and STEMI)
Mechanism of Action	Inhibits platelet P2Y12 adenosine diphosphate receptor		
Reversible?	No	No	Yes
Prodrug?	Yes	Yes	No
How Supplied	Tablets: 75mg; 300mg	Tablets: 5mg; 10mg	Tablets: 90mg
Administration	Orally once-daily	Orally once-daily	Orally twice-daily
Drug Interactions	CYP2C19 inhibitors; NSAIDs; warfarin	NSAIDs; warfarin	Strong CYP3A inhibitors or inducers; simvastatin; lovastatin; digoxin
Contraindications	Active pathological bleeding; hypersensitivity to clopidogrel	Active pathological bleeding; prior TIA or stroke; hypersensitivity to prasugrel	History of intracranial hemorrhage; active pathological bleeding
Maintenance WAC/Day	$0.27	$6.955	$7.909

Table 2 PLATO: CV Death, MI, Stroke by Maintenance Aspirin Dose Inside and Outside the United States[18,23]

Region	ASA Dose (mg)	Ticagrelor		Clopidogrel		HR (95% CI)
		N	E	N	E	
U.S.	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100-<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-U.S.	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100-<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7,449	546	7,443	699	0.78 (0.69, 0.87)

Hazard ratios (HR) and associated 95% confidence intervals (CI) comparing ticagrelor and clopidogrel for the primary efficacy outcome according to region (United States and the rest of the world [non-U.S.] and dose category for median maintenance aspirin [ASA] dose). *N* denotes number of patients; *E*, number of events. *HR was not calculated owing to the small number of events.

Step edits, prior authorizations, and high cost sharing may limit the ability of patients to fill certain prescriptions in a timely manner. Barriers like this can result in medication discontinuation directly following hospital discharge.

Additionally, discharge planning and patient education remains a problematic area. Many patients leave the hospital without a firm understanding of what their next steps should be, what medications they should be getting filled and why, and when to follow-up with their physicians. If patients are to be initiated on ticagrelor, it is important they are aware of the differences between aspirin dosages. In the minds of many patients, "baby aspirin" is not for adults and there is a perception that a higher dose would lead to better health. Hospital discharge staff and those conducting medication reconciliation should be focusing on overcoming this perception, educating patients, working to ensure access to the appropriate medications, and providing strategies for prolonged adherence.

ACS patients can be challenging to appropriately manage and costly to health plans. Although the ultimate goal is to reduce the rate of recurrent cardiac events, it is important to consider the cost of pharmaceuticals as well. These patients typically require multiple medications and may have several concomitant disease states. Finding the most clinically appropriate and cost-effective medications is important. For many patients with ACS, clopidogrel will remain a viable and relatively inexpensive choice. However, access to more potent and consistent pharmacologic treatment options, such as ticagrelor, should be readily available to patients, especially those demonstrating high risk factors for cardiovascular events (e.g., troponin positive).

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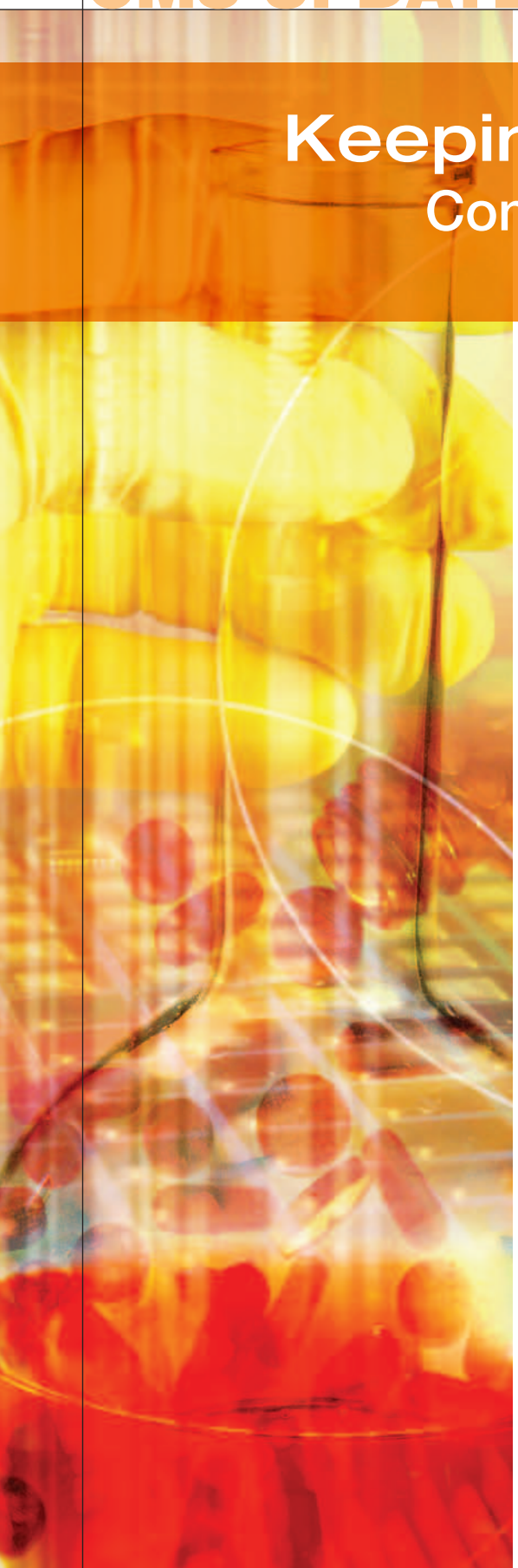

Keeping Up with Medicare:
Considerations for Managed Care

Judith S. Hurley, MS, RD

In the swiftly evolving world of healthcare, it is crucial to stay at the forefront of Medicare trends and changes. The following is a roundup of some important topics relating to Medicare, including upcoming changes in the Centers for Medicare & Medicaid Services' (CMS) Star Ratings program, the first-ever assessment of the relationship between quality ratings and enrollment in Medicare Advantage plans with prescription drug coverage (MA-PD), and an update on Medicare Part D medication therapy management (MTM) programs.

Proposed Changes to the CMS Star Ratings

Another year brings more tweaks and changes to the CMS Star Ratings program. This 5-star quality rating system evaluates Medicare Advantage (MA) plans and Medicare Prescription Drug Plans (PDPs) on a variety of categories, including preventive medicine, chronic disease management, and patient satisfaction. The proposed changes for 2014 (and some for 2015) were released for comment in November 2012 and the final call letter was made available in April of this year.[1-3]

The key upcoming changes are summarized in Table 1 (page 48). Changes to the specifications or calculations of four current measures, along with new rounding rules for most measures, are being initiated in 2014 or 2015. Increases in the existing 4-star thresholds (the level that defines a high-quality plan) are on the horizon for several measures in 2015. Although the first-time implementation of 4-star thresholds for 11 measures had been proposed for 2014, CMS has put this on hold based on feedback received from plan sponsors. Because the star thresholds are based on statistical analysis and the relative ranking of plan scores, they are not determined until at least two years of historical data are available for a specific measure. Although the 11 measures meet that two-year requirement, CMS has decided to conduct a more comprehensive analysis of the potential impact on plan scoring before moving forward with the new thresholds.

To encourage consistent improvement in quality of care across both Part C and D measures, CMS plans to make it harder for poorly performing plans to avoid being disadvantaged by the Low Performer Icon (LPI). This icon is displayed next to a plan's name on the CMS website, where it can be seen by beneficiaries seeking plan information. Currently, the icon is assigned to plans receiving less than 3 stars for their Part C or D sum-

mary ratings for the past three consecutive years. The algorithm is rather forgiving, however. Plans that switch back and forth between poor performance in Part C one year and poor performance in Part D another year do not receive the LPI. Going forward, CMS will assign the icon to contracts receiving 2.5 stars or fewer for any combination of their Part C and D summary ratings for three consecutive years.[3]

In its ongoing effort to improve the ratings system, CMS also has been evaluating strategies for reducing the risk of misclassifying a plan's performance (in other words, the risk that the rating does not reflect the plan's "true" performance). This misclassification can potentially occur when ratings on individual measures are averaged to derive summary scores. For example, currently, two plans can both achieve a Breast Cancer Screening summary score of 2 stars, even though one plan's actual measure score is 47 percent and the other's is 63 percent—a difference of 16 percentage points.[2] Using actual percentage scores rather than summary scores in calculating overall plan ratings would better reflect this considerable difference in performance, according to CMS. The risk of misclassifying performance is greater for low-enrollment plans, which will be included in the Star Ratings program for the first time in 2015, but any misclassification could potentially affect all plans, since a plan's rating for an individual measure depends on the distribution of scores among all plans.[1] Although CMS ultimately decided not to make changes to score calculations for 2014, these changes can be expected in future revisions.[3] For complete details about these and other upcoming or proposed changes to the CMS Star Ratings, see the final 2014 call letter for Medicare Advantage Plans, available at **www.cms.gov.**[3]

Higher Quality Ratings Boost Medicare Advantage Plan Enrollment

Rating health plans for quality matters greatly to insurers, employers, and policy makers, but what about consumers? It has been unclear whether consumers utilize quality ratings when selecting a health plan. In a study published recently in *JAMA*, researchers at CMS reported that Medicare beneficiaries are relying on CMS Star Ratings when choosing a Medicare Advantage plan with prescription drug coverage (MA-PD).[5]

The study examined the plan selections of nearly 1.3 million new enrollees and enrollees who switched plans in 2011, or about 17 percent of the nation's 7.6 million Medicare beneficiaries who are eligible for MA-PD enrollment. New enrollees had an average of 16.7 plans to choose from, of which an average of 2.0 plans were rated 4 stars or higher. Enrollees switching plans chose from an average of 17.3 plans, of which an average of 1.7 plans were rated 4 stars or higher.

Higher star ratings were associated with an increased likelihood of enrollment. Specifically, every 1-star increase in quality was associated with a 9.5 percent greater likelihood of enrollment among new enrollees. Among enrollees switching plans, every 1-star increase was associated with a 4.4 percent greater likelihood of enrollment. The analysis controlled for a number of factors that affect plan selection, including premiums, estimated out-of-pocket costs, the plan's local market share, and demographic characteristics of beneficiaries.

Star ratings were more closely associated with plan enrollment among whites compared to other races/ethnicities. Although the association was still positive, the ratings seemed to have less impact on the youngest enrollees, those with low income, and beneficiaries living in rural areas or the Midwest. Lead author Rachel Reid and her colleagues at CMS suggest that rural or low-income beneficiaries may give more weight to clinician proximity, premiums, and other costs than to quality ratings when selecting a plan. However, among the entire sample, higher star ratings were associated with greater likelihood of plan enrollment, in spite of higher premiums.

Improving MTM Programs

It is estimated that 1.5 million preventable, medication-related adverse events occur each year and cost billions of dollars annually.[5] Not surprisingly, CMS is pushing Medicare Part D plans to implement stronger MTM programs. These programs aim to optimize drug therapy and related patient outcomes by assessing an individual's drug regimen, monitoring drug safety and efficacy, and improving patient adherence to the drug regimen, among other activities.

Table 1 **Key Upcoming and Proposed Changes in CMS Star Ratings***

Current Measure or Method	Upcoming Changes	
Call Center—Foreign Language Interpreter and TTY/TDD Availability (Part C and Part D)	For Puerto Rico plans only, beginning in 2013, the metric is revised to count English as a foreign language to reflect the fact that Spanish is the predominant language in Puerto Rico.	
Quality Improvement (Part C and Part D)	Plans achieving an overall rating of 4 or more stars, or 5 stars in two years on an individual measure, and that experience a decline in the measure's score will have the measure excluded from their improvement calculation. Currently, this "hold harmless" provision applies only to plans achieving an overall rating of 4 or more stars. To be eligible for the provision, plans must provide data for at least half of the quality improvement measures. Additionally, improvement scores of 0 will receive 3 stars.	
High Risk Medication Use (Part D)	The updated Pharmacy Quality Alliance (PQA) list of High Risk Medications will be applied to calculate the High Risk Medication (HRM) measure for 2015 (using 2013 data). Also, changes in Part D coverage, including coverage of barbiturates (which are not on the PQA list), will be reflected in the 2015 measure calculations. The measure's technical notes have also been clarified.	
Medication Adherence for Diabetes Medications (Part D)	Two drug classes (meglitinides and incretin mimetic agents) are being added to the four classes currently included in the measure. This change will be adopted for the 2015 Star Ratings (using 2013 data). As the new drug classes are injectables, the measure's name has been changed to remove the reference to oral medications.	
Rounding of Measure Data	Measure data and cut points for star ratings will be rounded to whole numbers to avoid small differences in decimal values that result in differences in performance ratings. Exceptions are the Appeals Auto-forward (Part D), Complaints, and Improvements categories, which will be rounded to one, two, and three decimal points, respectively.	
Proposed New Measure		
Disenrollment Reasons	New measures related to the primary reason for disenrollment are being considered for 2015. To inform the decision, CMS is conducting a random survey of recent disenrollees from Medicare Advantage and Prescription Drug Plans in 2013.	
Proposed Changes to Existing 4-Star Thresholds		
Cardiovascular Care—Cholesterol Screening	Controlling Blood Pressure	Diabetes Treatment
Medication Adherence for Diabetes Medications	Medication Adherence for Hypertension (RAS Antagonists)	Medication Adherence for Cholesterol (Statins)
An increase of 2% in the 4-star threshold is proposed for these measures in 2015. The measures are relevant to the Million Hearts Campaign, a national initiative to prevent 1 million heart attacks and strokes by 2017, which CMS is supporting.[3]		
Under Consideration: New 4-Star Thresholds		
Adult BMI Assessment	COA—Medication Review	COA—Functional Status Assessment
COA—Pain Screening	Pain—All-cause Readmissions	Complaints
Audit	Voluntary Disenrollment	Medication Adherence for Diabetes Medications
Medication Adherence for Hypertension (RAS Antagonists)	Medication Adherence for Cholesterol (Statins)	
The implementation of 4-star thresholds for these existing measures (initially proposed for 2014) is being delayed until CMS completes further analysis.[3]		

Key: COA=Care for Older Adults; Part C=Medicare Advantage Plan; Part D=Medicare prescription drug coverage; RAS=renin angiotensin system
*Proposed changes apply to 2014 Star Ratings unless otherwise noted. Note that calculation of star ratings for a given year is based on plan data from two years prior. Please refer to CMS sources for complete details of measure specifications and calculations.
Source: Announcement of Calendar Year (CY) 2014 Medicare Advantage (MA) Capitation Rates and Medicare Advantage and Part D Payment Policies and Final Call Letter. Centers for Medicare & Medicaid Services. 1 April 2013.

"Higher star ratings were associated with an increased likelihood of enrollment. Specifically, every 1-star increase in quality was associated with a 9.5 percent greater likelihood of enrollment among new enrollees."

Although the findings are preliminary, the researchers concluded that "publicly reported star ratings could be achieving one of their intended purposes of guiding beneficiaries toward higher-quality plans." High-quality MA-PD plans already qualify for financial bonuses and enrollment window benefits from CMS. This first large assessment of the relationship between quality ratings and plan selection by beneficiaries suggests there is an additional incentive for plans to pursue higher quality.[5]

CMS Urges Greater Use of Medication Therapy Management Programs

It is estimated that 1.5 million preventable medication-related adverse events occur each year and cost billions of dollars annually.[5] Not surprisingly, CMS is pushing Medicare Part D plans to implement stronger MTM programs. These programs aim to optimize drug therapy and related patient outcomes by assessing an individual's drug regimen, monitoring drug safety and efficacy, and improving patient adherence to the drug regimen, among other activities. According to CMS guidelines, the programs must target individuals with three or more chronic diseases, eight or more prescription medications, and high annual prescription drug costs (at least $3,144 in 2013).[7]

A key task of MTM programs is conducting a comprehensive medication review (CMR) for each participant. Part D plans have some flexibility in setting the eligibility criteria for MTM programs, and CMS has concerns that some plan sponsors might be taking advantage of this flexibility by unduly restricting program eligibility in order to reduce their CMR workloads.[6,7] In fact, enrollment has been reported to be as low as 10-13 percent of PDP members, with CMRs performed for only 1 percent.[6]

Performance of MTM is measured as the rate of completion of comprehensive medication reviews (CMR) among MTM-eligible patients.[2] Although CMS considered adding an MTM measure to the 2014 Star Ratings, this has been delayed until 2015. Beginning this year, however, the MTM performance of Part D plans will be displayed on the CMS website, even though the score is not yet part of the overall Star Ratings calculation. Note that long-term care residents have been excluded from the measure in previous years, but this will not be the case going forward. As of 2013, all beneficiaries enrolled in an MTM program must be offered a CMR at least annually, regardless of the setting.[7]

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PIPELINE TRENDS

NEW DRUG APPROVALS			
Drug	**Manufacturer**	**Approval Date**	**Indication**
Ravicti™ (glycerol phenylbutyrate) oral liquid	Hyperion	February 1, 2013	Nitrogen-binding agent for the chronic management of patients with urea cycle disorders
Pomalyst® (pomalidomide) capsule	Celgene	February 8, 2013	Thalidomide analogue indicated for the treatment of patients with multiple myeloma
Kadcyla™ (ado-trastuzumab emtansine) injection	Genentech	February 22, 2013	HER2-targeted antibody and microtubule inhibitor conjugate for the treatment of patients with HER2-positive, metastatic breast cancer
Osphena™ (ospemifene) tablet	Shionogi	February 26, 2013	Estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia due to menopause
Tecfidera™ (dimethyl fumarate) capsule	Biogen	March 27, 2013	Nrf2 pathway activator for the treatment of relapsing forms of multiple sclerosis
Karbinal ER™ (carbinoxamine) oral suspension	Tris	March 28, 2013	H1 receptor antagonist indicated for the symptomatic treatment of seasonal and perennial allergic rhinitis
Invokana™ (canagliflozin) tablet	Janssen	March 29, 2013	Selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of Type 2 Diabetes
Diclegis® (doxylamine and pyridoxine) tablet	Duchesnay	April 8, 2013	Antihistamine and vitamin B6 analog combination indicated for the treatment of nausea and vomiting in pregnant women
Simbrinza™ (brimonidine and brinzolamide) opthalmic suspension	Alcon	April 19, 2013	Alpha 2 adrenergic receptor agonist and carbonic anhydrase inhibitor indicated for the reduction of elevated intraocular pressure
Procysbi™ (cysteamine bitartrate) delayed-release capsule	Raptor Pharmaceutical Corp.	April 30, 2013	Cystine depleting agent indicated for the treatment of nephropathic cystinosis
Breo Ellipta™ (fluticasone and vilanterol) Inhalation powder	GlaxoSmithKline and Theravance	May 10, 2013	Inhaled corticosteroid/long-acting beta2 agonist combination indicated for the treatment of patients with COPD
Nymalize™ (nimodipine) oral solution	Arbor	May 10, 2013	Calcium channel blocker indicated to improve neurological outcomes following subarachnoid hemorrhage
Xofigo® (radium Ra 223 dichloride) injection	Bayer HealthCare	May 15, 2013	Alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer
Mekinist™ (trametinib) tablet	GlaxoSmithKline	May 29, 2013	Kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations
Tafinlar® (dabrafenib) capsule	GlaxoSmithKline	May 29, 2013	Kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations
Bloxiverz (neostigmine methylsulfate) injection	Flamel Technologies	May 31, 2013	Cholinesterase inhibitor used for the reversal of the effects of non-depolarizing neuromuscular blocking agents

NEW FDA-APPROVED INDICATIONS		
Drug	**Approval Date**	**Indication**
Tamiflu® (oseltamivir phosphate)	December 21, 2012	Updated to now treat children younger than 1 year
Botox® (onabotulinumtoxinA)	January 18, 2013	Approved to treat overactive bladder
Exjade® (deferasirox)	January 23, 2013	Expanded approval to treat patients ages 10 years and older who have chronic iron overload resulting in non-transfusion-dependent thalassemia (NTDT)
Gleevec® (imatinib)	January 25, 2013	Approved new use to treat children newly diagnosed with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)
Epiduo® (adapalene/benzoyl peroxide)	February 1, 2013	Updated to treat acne in children as young as 9 years
Stivarga® (regorafenib)	February 25, 2013	Expanded approval to treat patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other treatments
Actemra® (tocilizumab)	April 30, 2013	Approved to treat polyarticular juvenile idiopathic arthritis in children 2 years and older with active disease
Simponi® (golimumab)	May 15, 2013	Approved for treatment of moderate to severe ulcerative colitis in adults
Revlimid® (lenalidomide)	June 5, 2013	Approved for relapsed or refractory mantle cell lymphoma

Disclosures: The information contained in Pipeline Trends is current as of June 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	Advertised Advantage
Delzicol™ (mesalamine)	February 5, 2013	Easier-to-swallow capsule formulation of mesalamine to replace Asacol
Vituz® (hydrocodone bitartrate and chlorpheniramine maleate)	February 20, 2013	Antihistamine/antitussive combination indicated for the relief of cough and symptoms associated with upper-respiratory allergies or a common cold
Abilify Maintena™ (aripiprazole)	February 28, 2013	Once-monthly extended-release injectable suspension for the treatment of schizophrenia
TOBI® Podhaler™ (tobramycin)	March 22, 2013	Antibacterial aminoglycoside indicated for the management of cystic fibrosis patients with Pseudomonas aeruginosa
Aciphex® Sprinkle™ (rabeprazole)	March 26, 2013	Treatment of gastroesophageal reflux disease (GERD) in children 1 to 11 years old for up to 12 weeks
Sitavig® (acyclovir)	April 2, 2013	Mucoadhesive buccal tablet formulation of the antiviral drug acyclovir indicated for the treatment of recurrent orofacial herpes (cold sores)
Prolensa™ (bromfenac)	April 5, 2013	Topical NSAID for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Liptruzet™ (atorvastatin and ezetimibe)	May 3, 2013	Oral statin (HMG-CoA reductase inhibitor) and cholesterol absorption inhibitor combination indicated for the treatment of hyperlipidemia

GENERIC DRUG APPROVALS

Drug	Approval
Rosiglitazone (Avandia®)	January 25, 2013
Doxorubicin (Doxil®)	February 4, 2013
Mafenide acetate (Sulfamylon®)	February 12, 2013
Buprenorphine HCl/Naloxone HCl Dihydrate (Suboxone®)	February 25, 2013
Travoprost (Travatan®)	March 1, 2013
Desvenlafaxine (Pristiq®)	March 4, 2013
Zoledronic acid (Zometa®)	March 4, 2013
Mecamylamine (Inversine®)	March 19, 2013
Amlodipine and valsartan (Exforge®)	March 28, 2013
Acyclovir (Zovirax® ointment)	April 3, 2013
Acitretin (Soriatane®)	April 4, 2013
Prednisolone (Orapred ODT®)	April 10, 2013
Omeprazole and sodium bicarbonate (Zegerid® Powder)	April 19, 2013
Candesartan (Atacand®)	May 3, 2013
Zolmitriptan (Zomig®)	May 15, 2013

PROJECTED FIRST-TIME GENERIC ENTRY

Drug	Projected Generic Entry
Fenofibric acid (Trilipix®)	January 2014
Telmisartan (Micardis®/Micardis® HCT)	January 2014
Sirolimus tablet (Rapamune®)	January 2014
Norethindrone acetate and ethinyl estradiol (Loestrin® 24 Fe)	January 2014
Tolterodine tartrate (Detrol LA®)	January 2014
Moxifloxacin (Avelox®)	January 2014
Raloxifene hcl (Evista®)	February 2014
Sevelamer carbonate (Renvela®)	March 2014
Sirolimus solution (Rapamune®)	March 2014
Celecoxib (Celebrex®)	May 2014
Eszopiclone (Lunesta®)	May 2014
Esomeprazole (Nexium®)	May 2014
Glatiramer (Copaxone®)	May 2014
Risedronate (Actonel®)	June 2014
Tazarotene (Tazorac® gel)	June 2014
Capecitabine (Xeloda®)	June 2014

SUBOXONE® FILM VS. GENERIC BUPRENORPHINE/NALOXONE TABLETS
WAC/PACKAGE (30CT)

Product	Manufacturer	Strength			
		2-0.5mg	4-1mg	8-2mg	12-3mg
Suboxone® Film	Reckitt Benckiser	$117.85	$211.15	$211.15	$422.30
Buprenorphine HCl/naloxone HCl tablet	Actavis	$139.71	N/A	$250.39	N/A
Buprenorphine HCl/naloxone HCl tablet	Amneal	$139.81	N/A	$250.11	N/A
Buprenorphine HCl/naloxone HCl tablet	Avkare	$138.71	N/A	$250.11	N/A

Advancements in Cancer Treatment: A Double-Edged Sword

Recent breakthroughs in the development of pharmacologic therapies have resulted in substantial advancements in the treatment of many malignancies. A major focus for oncology research has been on identifying more specific molecular targets within malignant cells and developing pharmacologic products that can selectively mitigate tumor growth and proliferation. Targeted therapies provide exceptional improvements in progression-free and, at times, overall survival rates in malignancies, such as metastatic castration-resistant prostate cancer (mCRPC), renal cell carcinoma (RCC), and chronic myelogenous leukemia (CML).[1-3] Additionally, the newly approved therapies include several orally administered products that are relatively well-tolerated compared to alternative treatment options (i.e., IV chemotherapy).

As this era of targeted therapy continues to evolve, enthusiasm for therapeutic advancements is limited by the anticipated financial burden associated with these new products. Improved efficacy, tolerability, and convenience of oncology products have led to an unsustainable increase in the cost of treating various cancers. In fact, the cost of treating many malignancies has more than doubled in less than 10 years and these costs are expected to increase. For example, the U.S. Food and Drug Administration (FDA) approved 11 new molecular entities to treat cancers in 2012. Many of these new market entrants offer an overall survival benefit of two to four months over the previously available therapies but carry a price of more than $10,000 per patient per month.[4,5,6,7]

In an effort to control unnecessary utilization of expensive oncology products, organizations are beginning to evaluate strategies to manage the financial burdens associated with these medications. In 2012, Memorial Sloan-Kettering Cancer Center in New York made a highly controversial decision to not stock Zaltrap® (ziv-aflibercept; Sanofi), an expensive oncology drug.[8] Zaltrap, used in combination with 5-fluorouracil, leucovorin, and irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. Studies have demonstrated that Zaltrap offers almost the exact level of efficacy compared to previously available therapies, but at nearly double the cost. Taking cost into account for a new oncology drug was unusual for the hospital, but the cost was difficult to justify without an improvement in clinical outcomes. In response to this decision, the pharmaceutical manufacturer reduced the price of Zaltrap substantially. Regardless, this highlights the tipping point around value and the need for more appropriate strategies to improve cost-conscious care in the oncology arena.

For the majority of the drug approvals in the oncology market, it is difficult to compare new market entrants to previously available products due to a lack of head-to-head trials. For this reason, it may be difficult for managed care organizations to

Table 1

CML Tyrosine Kinase Inhibitor	Manufacturer	Dose	Annual Wholesale Acquisition Cost/Patient of TKI Therapy (in thousands)[12]							
			2005	2006	2007	2008	2009	2010	2011	2012
Gleevec® (Imatinib)[13]	Novartis	400mg QD	$29.3	$31.7	$34.2	$38.2	$44.4	$52.5	$60.6	$73.2
Sprycel® (Dasatinib)[14]	BMS	100mg QD	-	$53.7	$57.9	$62.7	$74.1	$87.6	$94.5	$100.5
Tasigna® (Nilotinib)[15]	Novartis	400mg BID	-	-	$69.4	$76.2	$87.2	$96.6	$99.6	$104.4
Bosulif® (Bosutinib)[16]	Pfizer	500mg QD	-	-	-	-	-	-	-	$98.1
Iclusig® (Ponatinib)[17]	Ariad	45mg QD	-	-	-	-	-	-	-	$114.9

limit reimbursement for certain oncology medications. However, it is important to remember that there are other avenues of oncology management that can be explored as mechanisms to contain costs and improve outcomes.

One such example is in the treatment of CML. Since 2001, several oral tyrosine kinase inhibitors (TKIs) have been approved to treat this condition. Although these products have demonstrated clinical efficacy and extend progression-free survival, the cost of these medications creates a financial challenge for payors. An opportunity to promote cost-effective care by optimizing appropriate therapy may exist for management of CML. As CML is largely an asymptomatic disease state, response to therapy is difficult to assess without conducting the appropriate laboratory tests. This is important for payors to understand, as up to 30 percent of patients will fail initial imatinib therapy. By requiring that physicians comply with the monitoring recommendations outlined in the National Comprehensive Cancer Network (NCCN) guidelines, payors can limit wasted costs and negative outcomes by ensuring that their members are responding to the prescribed CML therapy. At this point, patients should be assessed to determine the reason for therapeutic failure. Two of the most prominent reasons are nonadherence and the development of molecular mutations. If a patient has been adherent to his or her CML therapy and does not meet the target response, he or she may be an appropriate candidate for a therapy modification (i.e., medication switch). However, it might not be appropriate to simply recommend the next least costly agent as second-line therapy. Patients with CML often develop resistance to TKIs from the development of molecular mutations. Fortunately, if a patient is not responding to his or her current therapy, physicians can test for potential mutations and modify therapy accordingly. Each of the TKIs used to treat CML has a different efficacy profile in terms of treating patients with various mutations, and it is important to choose the most appropriate product to increase the likelihood of achieving a complete response.[9,10,11]

This is only one example of potential cost-conscious strategies in the management of oncology. With the continued increase in pharmaceutical costs, optimizing value, including adherence to NCCN guidelines, patient-provider shared decision-making, and best practices in care coordination will have to be refined to improve outcomes while remaining sensitive to the economic implications.

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Low rates of hypoglycemia

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

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

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

Covered on more than 90% of managed care plans[2†]

Indications and Usage

Levemir® (insulin detemir [rDNA origin] injection) is indicated to improve glycemic control in adults and children with diabetes mellitus.

Important Limitations of Use:
Levemir® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

Important Safety Information

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

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

Hypoglycemia is the most common adverse reaction of insulin therapy, including Levemir®. The timing of hypoglycemia usually reflects the time action profile of the administered insulin formulations. Glucose monitoring is essential for all patients receiving insulin therapy. Any changes to an insulin regimen should be made cautiously and only under medical supervision.

Needles and Levemir® FlexPen® must not be shared.

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

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

Please see brief summary of Prescribing Information on adjacent page.

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

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

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

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

Levemir® FlexPen®
insulin detemir (rDNA origin) injection

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

novo nordisk®

LEVEMIR® (insulin detemir [rDNA origin] injection)

Rx ONLY

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

INDICATIONS AND USAGE: LEVEMIR® is indicated to improve glycemic control in adults and children with diabetes mellitus. Important Limitations of Use: LEVEMIR® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

CONTRAINDICATIONS: LEVEMIR® is contraindicated in patients with hypersensitivity to LEVEMIR® or any of its excipients. Reactions have included anaphylaxis.

WARNINGS AND PRECAUTIONS: Dosage adjustment and monitoring: Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment. As with all insulin preparations, the time course of action for LEVEMIR® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity. **Administration:** LEVEMIR® should only be administered subcutaneously. Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycemia. Do not use LEVEMIR® in insulin infusion pumps. Do not dilute or mix LEVEMIR® with any other insulin or solution. If LEVEMIR® is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR® and the mixed insulin may be altered in an unpredictable manner. **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR®. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia. The prolonged effect of subcutaneous LEVEMIR® may delay recovery from hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. **Hypersensitivity and allergic reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR®. **Renal Impairment:** No difference was observed in the pharmacokinetics of insulin detemir between non-diabetic individuals with renal impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal impairment. **Hepatic Impairment:** Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment. **Drug interactions:** Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia.

ADVERSE REACTIONS: The following adverse reactions are discussed elsewhere: Hypoglycemia; Hypersensitivity and allergic reactions. Clinical trial experience: Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1-4 below. See Tables 5 and 6 for the hypoglycemia findings.

Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 767)	NPH, % (n = 388)
Upper respiratory tract infection	26.1	21.4
Headache	22.6	22.7
Pharyngitis	9.5	8.0
Influenza-like illness	7.8	7.0
Abdominal Pain	6.0	2.6

Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR® to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 161)	Glargine, % (n = 159)
Upper respiratory tract infection	26.7	32.1
Headache	14.3	19.5
Back pain	8.1	6.3
Influenza-like illness	6.2	8.2
Gastroenteritis	5.6	4.4
Bronchitis	5.0	1.9

Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 432)	NPH, % (n = 437)
Upper respiratory tract infection	12.5	11.2
Headache	6.5	5.3

Table 4: Adverse reactions (excluding hypoglycemia) in a 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 232)	NPH, % (n = 115)
Upper respiratory tract infection	35.8	42.6
Headache	31.0	32.2
Pharyngitis	17.2	20.9
Gastroenteritis	16.8	11.3
Influenza-like illness	13.8	20.9
Abdominal pain	13.4	13.0
Pyrexia	10.3	6.1
Cough	8.2	4.3
Viral infection	7.3	7.8
Nausea	6.5	7.0
Rhinitis	6.5	3.5
Vomiting	6.5	10.4

Hypoglycemia: Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR®. Tables 5 and 6 summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR® clinical trials. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a blood glucose below 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (<50 mg/dL in Study A and C) that was self-treated by the patient. The rates of hypoglycemia in the LEVEMIR® clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR®-treated patients and non-LEVEMIR®-treated patients (see Tables 5 and 6).

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

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

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

		Study E Type 2 Diabetes Adults 24 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 22 weeks In combination with insulin aspart	
		Twice-Daily LEVEMIR®	Twice-Daily NPH	Once- or Twice Daily LEVEMIR®	Once- or Twice Daily NPH
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	2.5 (6/238)	1.5 (3/195)	4.0 (8/199)
	Event/patient/year	0.01	0.08	0.04	0.13
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	64.3 (153/238)	32.3 (63/195)	32.2 (64/199)
	Event/patient/year	3.5	6.9	1.6	2.0

Insulin Initiation and Intensification of Glucose Control: Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. *Lipodystrophy:* Long-term use of insulin, including LEVEMIR®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin adsorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy. *Weight Gain:* Weight gain can occur with insulin therapy, including LEVEMIR®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. *Peripheral Edema:* Insulin, including LEVEMIR®, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. *Allergic Reactions: Local Allergy:* As with any insulin therapy, patients taking LEVEMIR® may experience injection site reactions, including localized erythema, pain, pruritis, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR® reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy. Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks. *Systemic Allergy:* Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR®, and may be life-threatening. *Antibody Production:* All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LEVEMIR®, antibody development has been observed with no apparent impact on glycemic control. **Postmarketing experience:** The following adverse reactions have been identified during post approval use of LEVEMIR®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Medication errors have been reported during post-approval use of LEVEMIR® in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR®. To avoid medication errors between LEVEMIR® and other insulins, patients should be instructed always to verify the insulin label before each injection.

More detailed information is available upon request.

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Revised: 1/2012

0212-00007333-1 2/2012

novo nordisk®

Levemir®
insulin detemir (rDNA origin) injection

Victoza® (liraglutide [rDNA origin] injection)

Rx Only

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

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

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

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

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications]*. In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there were 7 cases of pancreatitis among Victoza®-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza® were reported as acute pancreatitis and two cases with Victoza® were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues *[see Adverse Reactions]*. **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

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

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

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

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

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

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

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

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

Gastrointestinal adverse events: In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In a 26-week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea overall gastrointestinal adverse event incidence rates, including nausea, were similar in patients treated with Victoza® and exenatide. In five clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In a 26 week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea, the proportion of patients with nausea also declined over time. *Immunogenicity:* Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia:* In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 4). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

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

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

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

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

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

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

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

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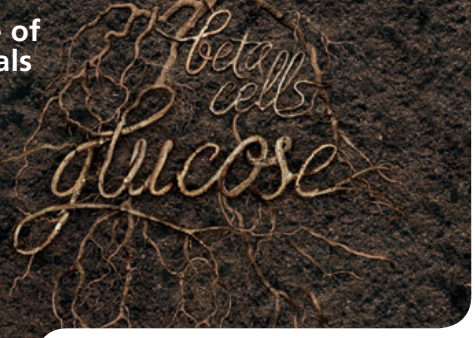
VICTOZA®
liraglutide (rDNA origin) injection

Help adult patients with type 2 diabetes gain greater access

Get to know Victoza® on a deeper level.

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



Low rate of hypoglycemia

Flexible dosing any time of day, independent of meals

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

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

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

VICTOZA®
liraglutide (rDNA origin) injection

Indications and usage

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

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

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

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

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

Important safety information

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

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

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

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

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

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

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

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

Please see brief summary of Prescribing Information on adjacent page.

*Victoza® 1.2 mg and 1.8 mg when used alone or in combination with OADs.
†Crossix ScoreBoard™ Report, September 2011. Adherence measured by number of actual Victoza® prescriptions filled for existing Victoza® patients enrolled in **VictozaCare™** versus a match-pair control group not enrolled in **VictozaCare™** through first 8 months of enrollment.

1111-00006045-1 January 2012

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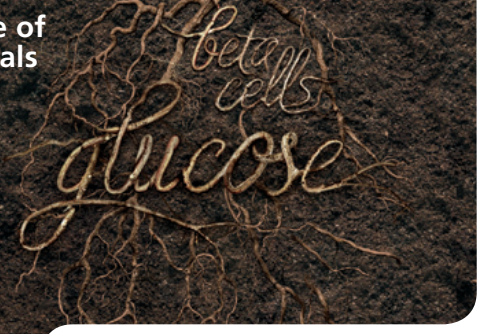

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