Urology Times®
The Leading News Source for Urologists
UrologyTimes.com
facebook.com/urologytimes
twitter.com/urologytimes

Urologists helping drive male-specific centers

Men's health clinics bring needed care under one roof

Lisette Hilton | UT CORRESPONDENT

National Report—Multidisciplinary men's health centers, rooted at hospitals, academic centers, and some private clinics, have expanded in the last few years and are meeting an important need in medicine, say key figures in these centers. Urologists are helping to drive these clinics' success.

True men's health centers do more than fill out prescriptions for testosterone, according to the experts we interviewed. To treat erectile dysfunction or low testosterone in isolation is irresponsible medicine, they said.

"Men's health is primarily viewed below the waistline—prostate issues, sexual health issues, fertility issues. And I think what we're starting to appreciate is that there are a lot of problems that really are above the waistline that are contributing to conditions below the waistline," said Steven Lamm, MD, an internal medicine physician and medical director of the Preston Robert Tisch Center for Men's Health at NYU Langone Medical Center, New York. "There's a movement and a trend toward a global care of men and trying to suggest that men really need to be taken care of in a holistic way. The urologic component really should be a component, but not the entire picture."

One of the hurdles to providing comprehensive health care for men, however, is that men are far less likely than women to go to the doctor. Urology could be the key to capturing this evasive gender. When men do visit a physician, it's often a urologist they see because urinary tract symptoms, erectile dysfunction, or infertility drive them to seek health care, according to James M. Hotaling, MD, MS, assistant professor of surgery (urology) and co-director of the Center for Reconstructive Urology and Men's Health, University of Utah, Salt Lake City.

"What we're moving toward is a model where these guys come in and essentially get all or most of their health care needs met in one visit," Dr. Hotaling said.

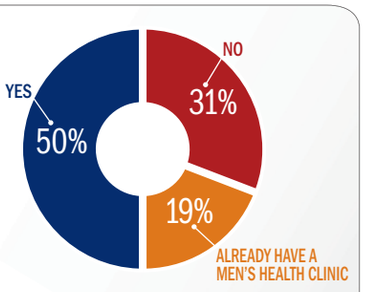
No shot clinics here

This model differs from the doc-in-a-box type of clinics described

Please see **CLINICS,** on page 41

UT asks

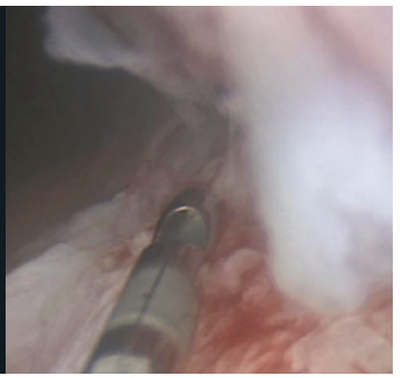
Are you considering broadening your practice to encompass a "men's health clinic"?



Source: *Urology Times* September 2014 online survey

PEEK INSIDE THE CLINICS

SLIDESHOW For a look at men's health clinics at NYU (right) and other leading institutions, see our slideshows at **bitly.com/UT-centers.**



ALSO INSIDE

MMC injections may end cycle of contracture Tx failures

See page 12

Inside THIS ISSUE

OCTOBER 2014
VOL. 42, NO. 11

Q&A
LOW-RISK PROSTATE CA
IAN THOMPSON, MD

Dr. Thompson discusses how his approach to low-risk disease, including screening and biopsy, has changed. **See page 20.**

VIAGRA® (sildenafil citrate) is indicated for the treatment of erectile dysfunction (ED).

IMPORTANT SAFETY INFORMATION

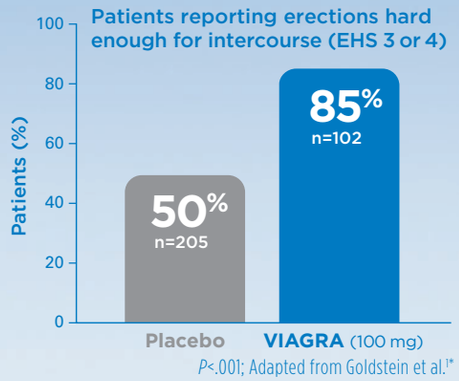
- **Nitrates:** Administration of VIAGRA to patients using nitric oxide donors, such as organic nitrates or organic nitrites in any form either regularly and/or intermittently is contraindicated. VIAGRA was shown to potentiate the hypotensive effect of nitrates.
- **Hypersensitivity Reactions:** VIAGRA is contraindicated in patients with a known hypersensitivity to sildenafil, as contained in VIAGRA and REVATIO, or any component of the tablet. Hypersensitivity reactions have been reported, including rash and urticaria.
- **Cardiovascular:** Patients should not use VIAGRA if sexual activity is inadvisable due to cardiovascular status. Physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by the vasodilatory effects of VIAGRA, especially in combination with sexual activity. There are no controlled clinical data on the safety or efficacy of VIAGRA in patients with the following characteristics: recent serious cardiovascular events, hypotension, or uncontrolled hypertension; if prescribed, this should be done with caution.
- **Prolonged Erection:** Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result. Use VIAGRA with caution in patients predisposed to priapism.
- **Effects on the Eye:** Patients should stop VIAGRA and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). VIAGRA should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION. There are no controlled clinical data on the safety or efficacy of VIAGRA in patients with retinitis pigmentosa.
- **Hearing Loss:** Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including VIAGRA. (It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.) Physicians should advise patients to stop taking PDE5 inhibitors, including VIAGRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing.

VGU639502-03 Printed in USA/June 2014

Pfizer U.S. Pharmaceuticals

LITTLE BLUE PILL.
HARDNESS MAKES A DIFFERENCE.

MEN SEE A DIFFERENCE WITH VIAGRA VS PLACEBO.



In a double-blind, placebo-controlled study of men with erectile dysfunction (ED) taking VIAGRA, erection hardness, as measured by the Erection Hardness Score (EHS), was a secondary end point.[1*]

The primary end point in this study was the effect of VIAGRA on erectile function, as measured by Q3 and Q4 of the International Index of Erectile Function (IIEF). Men taking VIAGRA showed significant improvement in penetration and erection maintenance.[1*]

The EHS is a validated instrument.[2]

Grade 1	Grade 2	Grade 3	Grade 4
Penis is larger but not hard	Penis is hard but not hard enough for penetration	Penis is hard enough for penetration but not completely hard	Penis is completely hard and fully rigid

IMPORTANT SAFETY INFORMATION (CONTINUED)

- **Potential Drug Interactions:** VIAGRA can potentiate the hypotensive effects of nitrates, alpha-blockers, and antihypertensives. Initiate VIAGRA at 25 mg with concomitant use of alpha-blockers.

  CYP3A4 inhibitors (eg, ritonavir, ketoconazole, itraconazole, erythromycin) increase VIAGRA plasma exposure. Do not exceed 25 mg of VIAGRA in a 48-hour period with ritonavir. Consider a starting dose of 25 mg of VIAGRA with erythromycin or strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, saquinavir).

  Decreased blood pressure, syncope, and prolonged erection may occur at higher sildenafil exposures.

- **Specific Populations:** Consider a starting dose of 25 mg of VIAGRA for patients age >65, patients with hepatic impairment or severe renal impairment.

- **Sexually Transmitted Diseases:** Use of VIAGRA offers no protection against sexually transmitted diseases, including the human immunodeficiency virus (HIV); therefore, physicians should consider counseling their patients about protective measures.

- **Adverse Reactions:** The most common adverse reactions (≥2%) with VIAGRA 25 mg, 50 mg, 100 mg vs placebo, respectively, include headache (16%, 21%, 28% vs 7%), flushing (10%, 19%, 18% vs 2%), dyspepsia (3%, 9%, 17% vs 2%), abnormal vision (1%, 2%, 11% vs 1%), nasal congestion (4%, 4%, 9% vs 2%), back pain (3%, 4%, 4% vs 2%), myalgia (2%, 2%, 4% vs 1%), nausea (2%, 3%, 3% vs 1%), dizziness (3%, 4%, 3% vs 2%), and rash (1%, 2%, 3% vs 1%).

*Results from the last 4 weeks of a double-blind, placebo-controlled, parallel-group, fixed-dose, as-needed study of patients with ED taking VIAGRA 25 mg, 50 mg, or 100 mg (N=532). Primary end point was change in erectile function as measured by Q3 and Q4 of the IIEF. Q3: "When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?" (Baseline: VIAGRA 100 mg=2.0, placebo=2.1; end point: VIAGRA 100 mg=4.0, placebo=2.2; *P*<.001 for all doses of VIAGRA vs placebo). Q4: "During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?" (Baseline: VIAGRA 100 mg=1.7, placebo=1.7; end point: VIAGRA 100 mg=3.9, placebo=2.1; *P*<.001 for all doses of VIAGRA vs placebo). Erection hardness was measured by patient-reported scoring on the EHS in the event log. Of patients taking VIAGRA 25 mg (n=97), 50 mg (n=105), and 100 mg (n=102), 72%, 80%, and 85% reported erections hard enough for sexual intercourse (EHS grade 3 or 4), respectively, compared with 50% of patients taking placebo (n=205; *P*<.001). EHS grade 1 indicates that the penis is larger but not hard; grade 2, that the penis is hard but not hard enough for penetration; grade 3, that the penis is hard enough for penetration but not completely hard; and grade 4, that the penis is completely hard and fully rigid.

Please see brief summary of full prescribing information for VIAGRA (25 mg, 50 mg, 100 mg) on the following pages.

References: 1. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA; for the Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med.* 1998;338 (20):1397-1404. **2.** Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the Erection Hardness Score. *J Sex Med.* 2007;4(6):1626-1634.

Brief summary of prescribing information

Please see package insert for full prescribing information.

VIAGRA®
(sildenafil citrate) tablets

INDICATION AND USAGE

VIAGRA is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Nitrates

Consistent with its known effects on the nitric oxide/cGMP pathway [*see Clinical Pharmacology (12.1, 12.2)*], VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using nitric oxide donors such as organic nitrates or organic nitrites in any form either regularly and/or intermittently is therefore contraindicated.

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely co-administered at this time point [*see Dosage and Administration (2.3), Drug Interactions (7.1), and Clinical Pharmacology (12.2)*].

Hypersensitivity Reactions

VIAGRA is contraindicated in patients with a known hypersensitivity to sildenafil, as contained in VIAGRA and REVATIO, or any component of the tablet. Hypersensitivity reactions have been reported, including rash and urticaria [*see Adverse Reactions (6.1)*].

WARNINGS AND PRECAUTIONS

Cardiovascular

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg), [*see Clinical Pharmacology (12.2)*]. While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Use with caution in patients with the following underlying conditions which can be particularly sensitive to the actions of vasodilators including VIAGRA – those with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.

There are no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP <90/50 mmHg) or hypertension (BP >170/110 mmHg);
- Patients with cardiac failure or coronary artery disease causing unstable angina.

Prolonged Erection and Priapism

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

VIAGRA should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia). However, there are no controlled clinical data on the safety or efficacy of VIAGRA in patients with sickle cell or related anemias.

Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥ 50. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2 fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [*see Adverse Reactions (6.2)*].

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including VIAGRA, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population, however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including VIAGRA, for this uncommon condition.

There are no controlled clinical data on the safety or efficacy of VIAGRA in patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including VIAGRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [*see Adverse Reactions (6.1), (6.2)*].

Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives

Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including VIAGRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may occur. In some patients, concomitant use of these two drug classes can lower blood pressure significantly [*see Drug Interactions (7.2) and Clinical Pharmacology (12.2)*] leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors. Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose [*see Dosage and Administration (2.3)*].
- In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Anti-hypertensives

VIAGRA has systemic vasodilatory properties and may further lower blood pressure in patients taking antihypertensive medications.

In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted [*see Drug Interactions (7.3) and Clinical Pharmacology (12.2)*].

Adverse Reactions with the Concomitant Use of Ritonavir

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (11-fold increase in AUC). If VIAGRA is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse reactions in patients taking ritonavir, a decrease in sildenafil dosage is recommended [*see Dosage and Administration (2.4), Drug Interactions (7.4), and Clinical Pharmacology (12.3)*].

Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies

The safety and efficacy of combinations of VIAGRA with other PDE5 Inhibitors, including REVATIO or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. Such combinations may further lower blood pressure. Therefore, the use of such combinations is not recommended.

Effects on Bleeding

There have been postmarketing reports of bleeding events in patients who have taken VIAGRA. A causal relationship between VIAGRA and these events has not been established. In humans, VIAGRA has no effect on bleeding time when taken alone or with aspirin. However, *in vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). In addition, the combination of heparin and VIAGRA had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Counseling Patients About Sexually Transmitted Diseases

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

ADVERSE REACTIONS

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

- Cardiovascular [*see Warnings and Precautions (5.1)*]
- Prolonged Erection and Priapism [*see Warnings and Precautions (5.2)*]
- Effects on the Eye [*see Warnings and Precautions (5.3)*]
- Hearing Loss [*see Warnings and Precautions (5.4)*]
- Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives [*see Warnings and Precautions (5.5)*]
- Adverse Reactions with the Concomitant Use of Ritonavir [*see Warnings and Precautions (5.6)*]
- Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies [*see Warnings and Precautions (5.7)*]
- Effects on Bleeding [*see Warnings and Precautions (5.8)*]
- Counseling Patients About Sexually Transmitted Diseases [*see Warnings and Precautions (5.9)*]

The most common adverse reactions reported in clinical trials (≥ 2%) are headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash.

Clinical Trials Experience

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

VIAGRA was administered to over 3700 patients (aged 19-87 years) during pre-marketing clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse reactions for VIAGRA (2.5%) was not significantly different from placebo (2.3%).

In fixed-dose studies, the incidence of some adverse reactions increased with dose. The type of adverse reactions in flexible-dose studies, which reflect the recommended dosage regimen, was similar to that for fixed dose studies. At doses above the recommended dose range, adverse reactions were similar to those detailed in Table 1 below but generally were reported more frequently.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with VIAGRA and More Frequent than Placebo in Fixed-Dose Phase II/III Studies

Adverse Reaction	25 mg (n=312)	50 mg (n=511)	100 mg (n=506)	Placebo (n=607)
Headache	16%	21%	28%	7%
Flushing	10%	19%	18%	2%
Dyspepsia	3%	9%	17%	2%
Abnormal vision†	1%	2%	11%	1%
Nasal congestion	4%	4%	9%	2%
Back pain	3%	4%	4%	2%
Myalgia	2%	2%	4%	1%
Nausea	2%	3%	3%	1%
Dizziness	3%	4%	3%	2%
Rash	1%	2%	3%	1%

†Abnormal Vision: Mild to moderate in severity and transient, predominantly color tinge to vision, but also increased sensitivity to light, or blurred vision.

When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials of two to twenty-six weeks duration, patients took VIAGRA at least once weekly, and the following adverse reactions were reported:

Table 2: Adverse Reactions Reported by ≥2% of Patients Treated with VIAGRA and More Frequent than Placebo in Flexible-Dose Phase II/III Studies

Adverse Reaction	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal congestion	4%	2%
Abnormal Vision†	3%	0%
Back pain	2%	2%
Dizziness	2%	1%
Rash	2%	1%

†Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a Whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal

electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

Analysis of the safety database from controlled clinical trials showed no apparent difference in adverse reactions in patients taking VIAGRA with and without anti-hypertensive medication. This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of VIAGRA. 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. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and cerebrovascular

Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors [*see Warnings and Precautions (5.1) and Patient Counseling Information (17.3)*].

Hemic and Lymphatic: vaso-occlusive crisis: In a small, prematurely terminated study of REVATIO (sildenafil) in patients with pulmonary arterial hypertension (PAH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported in patients who received sildenafil than in those randomized to placebo. The clinical relevance of this finding to men treated with VIAGRA for ED is not known.

Nervous: seizure, seizure recurrence, anxiety, and transient global amnesia.

Respiratory: epistaxis

Special senses:

Hearing: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including VIAGRA. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of VIAGRA, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors [*see Warnings and Precautions (5.4) and Patient Counseling Information (17.5)*].

Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal edema, retinal vascular disease or bleeding, and vitreous traction/detachment.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [*see Warnings and Precautions (5.3) and Patient Counseling Information (17.4)*].

Urogenital: prolonged erection, priapism [*see Warnings and Precautions (5.2) and Patient Counseling Information (17.6),* and hematuria.

DRUG INTERACTIONS

Nitrates

Administration of VIAGRA with nitric oxide donors such as organic nitrates or organic nitrites in any form is contraindicated. Consistent with its known effects on the nitric oxide/cGMP pathway, VIAGRA was shown to potentiate the hypotensive effects of nitrates [*see Dosage and Administration (2.3), Contraindications (4.1), Clinical Pharmacology (12.2)*].

Alpha-blockers

Use caution when co-administering alpha-blockers with VIAGRA because of potential additive blood pressure lowering effects. When VIAGRA is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating VIAGRA treatment and VIAGRA should be initiated at the lowest dose [*see Dosage and Administration (2.3), Warnings and Precautions (5.5), Clinical Pharmacology (12.2)*].

Amlodipine

When VIAGRA 100 mg was co-administered with amlodipine (5 mg or 10 mg) to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic [*see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)*].

Ritonavir and other CYP3A4 inhibitors

Co-administration of ritonavir, a strong CYP3A4 inhibitor, greatly increased the systemic exposure of sildenafil (11-fold increase in AUC). It is therefore recommended not to exceed a maximum single dose of 25 mg of VIAGRA in a 48 hour period [*see Dosage and Administration (2.4), Warnings and Precautions (5.6), Clinical Pharmacology (12.3)*].

Co-administration of erythromycin, a moderate CYP3A4 inhibitor, resulted in a 160% and 182% increases in sildenafil C_{max} and AUC, respectively. Co-administration of saquinavir, a strong CYP3A4 inhibitor, resulted in 140% and 210% increases in sildenafil C_{max} and AUC, respectively. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole could be expected to have greater effects than seen with saquinavir. A starting dose of 25 mg of VIAGRA should be considered in patients taking erythromycin or strong CYP3A4 inhibitors (such as saquinavir, ketoconazole, itraconazole) [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

Alcohol

In a drug-drug interaction study sildenafil 50 mg given with alcohol 0.5 g/kg in which mean maximum blood alcohol levels of 0.08% was achieved, sildenafil did not potentiate the hypotensive effect of alcohol in healthy volunteers [*see Clinical Pharmacology (12.2)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B.

VIAGRA is not indicated for use in women. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Risk summary

Based on animal data, VIAGRA is not predicted to increase the risk of adverse developmental outcomes in humans.

Animal data

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC.

Pediatric Use

VIAGRA is not indicated for use in pediatric patients. Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil resulting in approximately 84% and 107% higher plasma AUC values of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy young volunteers (18-45 years) [*see Clinical Pharmacology (12.3)*]. Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively [*see Clinical Pharmacology (12.3)*].

Of the total number of subjects in clinical studies of VIAGRA, 18% were 65 years and older, while 2% were 75 years and older. No overall differences in safety or efficacy were observed between older (≥ 65 years of age) and younger (< 65 years of age) subjects.

However, since higher plasma levels may increase the incidence of adverse reactions, a starting dose of 25 mg should be considered in older subjects due to the higher systemic exposure [*see Dosage and Administration (2.5)*].

Renal Impairment

No dose adjustment is required for mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment. In volunteers with severe renal impairment (Clcr<30 mL/min), sildenafil clearance was reduced, resulting in higher plasma exposure of sildenafil (~2 fold), approximately doubling of C_{max} and AUC. A starting dose of 25 mg should be considered in patients with severe renal impairment [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

Hepatic Impairment

In volunteers with hepatic impairment (Child-Pugh Class A and B), sildenafil clearance was reduced, resulting in higher plasma exposure of sildenafil (47% for C_{max} and 85% for AUC). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh Class C) have not been studied. A starting dose of 25 mg should be considered in patients with any degree of hepatic impairment [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse reactions were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Nitrates

Physicians should discuss with patients the contraindication of VIAGRA with regular and/or intermittent use of nitric oxide donors, such as organic nitrates or organic nitrites in any form [*see Contraindications (4.1)*].

Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should advise patients of the potential for VIAGRA to augment the blood pressure lowering effect of alpha-blockers and anti-hypertensive medications. Concomitant administration of VIAGRA and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, when VIAGRA is co-administered with alpha-blockers, patients should be stable on alpha-blocker therapy prior to initiating VIAGRA treatment and VIAGRA should be initiated at the lowest dose [*see Warnings and Precautions (5.5)*].

Cardiovascular Considerations

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician [*see Warnings and Precautions (5.1)*].

Sudden Loss of Vision

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including possible permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a "crowded" optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitor, including VIAGRA, for this uncommon condition [*see Warnings and Precautions (5.3) and Adverse Reactions (6.2)*].

Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including VIAGRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [*see Warnings and Precautions (5.4) and Adverse Reactions (6.2)*].

Priapism

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result [*see Warnings and Precautions (5.2)*].

Avoid Use with other PDE5 Inhibitors

Physicians should inform patients not to take VIAGRA with other PDE5 inhibitors including REVATIO or other pulmonary arterial hypertension (PAH) treatments containing sildenafil. Sildenafil is also marketed as REVATIO for the treatment of PAH. The safety and efficacy of VIAGRA with other PDE5 inhibitors, including REVATIO, have not been studied [*see Warnings and Precautions (5.7)*].

Sexually Transmitted Disease

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered [*see Warnings and Precautions (5.9)*].

LAB-0221-13.0 Revised: 03/2014

‘Men’s health’ more than a marketing ploy

A new emphasis on comprehensive, holistic care of men has emerged in the United States and elsewhere. As our cover article in this issue explains, urologists are helping to lead this charge.

Why the focus on men’s health, and why in 2014? Some say the answer is marketing, which may be partly true. After all, what better way to bring men into a medical practice than to offer one-stop shopping to address their urologic, cardiac, nutritional, and even psychological needs? This is the modus operandi of newer men’s health centers.

Richard R. Kerr

Kerr is group content director of *Urology Times*.

But there’s a more important reason these centers have taken hold. As urologists well know, men are reluctant visitors to the doctor’s office. The new centers simply fill a need, not only to bring men into the office but also to provide comprehensive care centered on their health and wellness.

Often, what brings them in is a urologic condition, such as erectile dysfunction. Cardiovascular disease, diabetes, obesity, and hypertension often coexist. Thus, the urologist can serve as an entry point for men’s overall care—the model on which many men’s health clinics are based.

Urologists also look to benefit. While some experts see a future for urologists as narrowly focused proceduralists, a more comprehensive, coordinated approach to male health could help reverse this fortune.

The urologist can serve as an entry point for men’s overall care.

Urology Times is committed to the men’s health trend and to helping you make the most of it. For starters, we have launched two new sections: #LetsTalkMensHealth, which features physician-authored, evidence-based articles on urologic and non-urologic conditions facing men; and ‘Y’tube, which covers surgical aspects of men’s health issues in a unique, video-based format. I am very pleased to introduce Steven A. Kaplan, MD, of Weill Cornell Medical Center, and James M. Hotaling, MD, MS, of the University of Utah, as the editorial leaders of #LetsTalkMensHealth and ‘Y’tube, respectively.

Going forward, look for additional content about the care of male patients, especially on our soon-to-be-redesigned website. You’ll find articles and more that “bust myths” about men’s medical issues, discuss holistic therapies in men’s health, explain how urology and primary care can work together in this endeavor, and much more.

At times, our new content will challenge you to think “beyond the pelvis.” Whether you are considering a dedicated men’s health center (our research shows half of you are) or simply want to improve the care you give your male patients, our goal is to provide the practical information and perspective you need to succeed.

Richard R. Kerr

Feedback

Send your comments to Kerr c/o *Urology Times*, at **UT@advanstar.com**

Urology Times

OCTOBER 2014 VOL. 41, NO. 11
The Leading News Source for Urologists
UrologyTimes.com

Mission

Urology Times takes the lead in providing news analysis of key advances in surgical and non-surgical techniques, treatments and practice management. As the #1 read publication reaching the full universe of specialists treating urologic disorders, *Urology Times* keeps urologists up to date so they can quickly provide better patient care while running a more efficient practice.

Content 24950 Country Club Blvd., Suite 200, North Olmsted, OH 44070 800-225-4569 | E-mail: UT@advanstar.com

Richard R. Kerr Group Content Director 440-891-2758 | dkerr@advanstar.com
Benjamin P. Saylor Content Editor 440-891-2780 | bsaylor@advanstar.com
Rob McGarr Group Art Director
Lecia Landis Art Director
Bob Gatty UT Washington Correspondent
Ray Painter, MD/Mark Painter Coding/Reimbursement Columnists

Advertising 485 Route 1, Building F, Suite 210, Iselin, NJ 08830

Georgiann DeCenzo | Executive Vice President | 440-891-2778 | gdecenzo@advanstar.com
Ken Sylvia | Vice President, Group Publisher | 732-346-3017 | ksylvia@advanstar.com
Samantha Armstrong | Publisher | 732-346-3083 | FAX: 732-596-0016 | sarmstrong@advanstar.com
Margie Jaxel | Dir. of Business Develpment, Healthcare Technology Sales | 732-346-3003 | mjaxel@advanstar.com
Patrick Carmody | Account Manager, Healthcare Technology | 440-891-2621 | pcarmody@advanstar.com
Joanna Shippoli | Account Manager, Recruitment Advertising | 440-891-2615 | jshippoli@advanstar.com
Don Berman | Business Director, eMedia | 212-951-6745, | dberman@advanstar.com
Meg Benson | Special Projects Director | 732-346-3039, | mbenson@advanstar.com
Gail Kaye | Director of Marketing & Research Services **Hannah Curis** | Sales Support
Renée Schuster | List Account Executive | 440-891-2613 | FAX: 440-891-2740 | rschuster@advanstar.com
Reprints: **Wright’s Media** 877-652-5295 ext. 121 / bkolb@wrightsmedia.com Outside US, UK, direct dial: 281-419-5725. Ext. 121
Permissions: **Maureen Cannon** 440-891-2742 | FAX: 440-891-2650 | mcannon@advanstar.com

Production ▪ Circulation 131 West First Street, Duluth, MN 55802-2065 Customer Service: 888-527-7008

Karen Lenzen | Senior Production Manager
Joy Puzzo | Audience Development Corporate Director
Christine Shappell | Audience Development Director
Wendy Bong | Audience Development Manager
Subscriber Customer Service: 218-740-6477 | FAX: 218-740-6437

Now Enrolling

BLADDER

A Study of **MPDL3280A** (an Engineered **Anti-PDL1** Antibody) in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer (UBC) (NCT02108652, Study ID GO29293)

A Phase II study for patients with locally advanced or metastatic UBC who are treatment-naïve and ineligible for cisplatin-based chemotherapy or have failed platinum-containing therapy

N=330

MPDL3280A[1]
(an engineered anti-PDL1 antibody)

Primary Endpoint:

- Objective response rate

Secondary Endpoints:

- Duration of response
- Progression-free survival
- Overall survival
- Safety: incidence of adverse events
- Incidence of antitherapeutic antibodies to MPDL3280A
- Maximum serum concentration (C_{max}) of MPDL3280A

Key Inclusion Criteria[2]:

- Documented locally advanced or metastatic transitional cell carcinoma of the urothelium
- Representative tumor specimens
- ECOG performance status of 0-1
- Life expectancy ≥12 weeks
- Measurable disease, as defined by RECIST v1.1
- Adequate hematologic and end-organ function
- Refractory or ineligible for platinum-based chemotherapy

Key Exclusion Criteria[2]:

- History of autoimmune disease
- Active hepatitis B or hepatitis C
- HIV-positive
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1
- Prior treatment with CD137 agonists, or immune checkpoint blockade therapies, including anti-CTLA4, anti-PD1, and anti-PDL1

For more information

Visit:	Call:	E-mail:
antiPDL1ClinicalTrials.com/hcp	Genentech Trial Information Support Line: **1-888-662-6728** (US only)	**global.rochegenentechtrials@roche.com**

1. Product under investigation has not been approved for use outside of the clinical trial setting. This information is presented only for the purpose of providing an overview of the clinical trial and should not be construed as a recommendation for use of any product for unapproved purposes.
2. For more information on trial inclusion and exclusion criteria, visit antiPDL1ClinicalTrials.com/hcp.

Genentech
A Member of the Roche Group

BIOONCOLOGY®

AACU LEGISLATIVE UPDATE

State Society conference shines light on leadership, advocacy

Leaders of state and national urologic societies heard just how important and impactful active physician participation in the political process is to the development of sensible health policy at the 2014 State Society Network Advocacy Conference recently hosted by the American Association of Clinical Urologists. Topic highlights included ACA insurance exchange plans, GME funding in the U.S., "supervised autonomy" for non-physician providers, and minimizing intrusions on the doctor-patient relationship, among many others.

READ ABOUT THESE MEETING HIGHLIGHTS AND MORE AT: *bitly.com/state-society*

BLOG

Lessons learned after a year in urology's 'real world'

The transition from residency to private practice was enlightening for urologist Henry Rosevear, MD. After a year in practice, he has learned valuable lessons about maintaining a professional appearance with patients (lose the "post-call" look), political correctness on the job (no more sarcasm), appreciating a great staff (count your blessings), why surgery is different when you're on your own (did I forget to close fascia?), and understanding the "business" of medicine (an ongoing challenge).

DR. ROSEVEAR

READ DR. ROSEVEAR'S BLOG AT: *bitly.com/Rosevear-lessons*

UT FOLLOWER OF THE MONTH

@VaibhavModgil

Vaibhav Modgil, BM, MRCS, social media editor of the *Journal of Clinical Urology,* is the *Urology Times* Twitter follower of the month! To be featured in this section, engage with us.

TWITTER.COM/UROLOGYTIMES

Our followers tweet about the ACA, vasectomy ads, more

Patrick Showalter
@pshowalter
Despite the #ACA, I am still caring for my patients. Caring for people can't be legislated. #urology

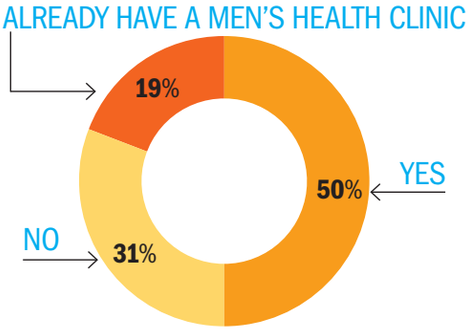
ben eddy
@DrBenEddy
What's the betting on time for Vip Patel's case at #erus14, my money is on 54min!! Excellence as always!

Nick Brook
@nickbrookMD
A Google ad I placed for vasectomy has been 'disapproved' by Google on basis of 'religion'. Odd that beheadings on YouTube are ok

Stephen Boorjian, MD
@SBoorjian
Honored and excited to be joining European Urology.

SEPTEMBER'S QUESTION OF THE MONTH

Are you considering broadening your practice to encompass a "men's health clinic"?



QUESTION FOR OCTOBER

Are more patients presenting with high-deductible plans?

Answer the survey online at *bitly.com/deductible-survey*

Urology Times Resource Center

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Videos, news, and more to help you manage your patients with advanced disease

http://urologytimes.com/CRPCA

LIKE US on Facebook and participate in the discussion.

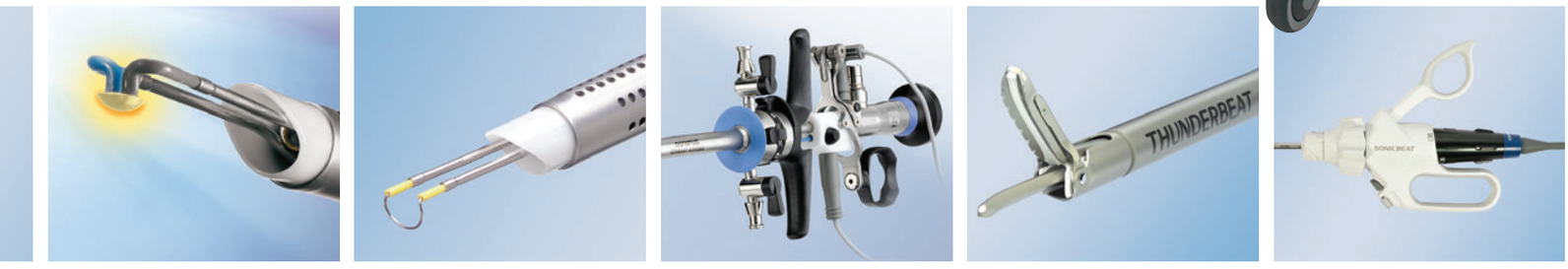
FACEBOOK.COM/UROLOGY TIMES

OLYMPUS®

Your Vision, Our Future

THUNDERBEAT

The World's **ONLY** Fully-Integrated Platform
Supporting BIPOLAR, MONOPOLAR
and ULTRASONIC Technology.



Perform TURP, TURBT, Nephrectomy, Cystectomy, Prostatectomy and more with the **THUNDERBEAT** System

For more information contact your local Olympus representative at 800-848-9024 or visit www.OlympusThunderbeat.com/urot

ADT overuse remains a problem among some urologists

Solo practitioners, non-academics more likely to use agents inappropriately

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Chapel Hill, NC—Inappropriate use of a gonadotropin-releasing hormone agonist (GnRHa) for androgen deprivation therapy (ADT) of localized prostate cancer fell dramatically following implementation of reimbursement cuts mandated by the Medicare Modernization Act of 2003, but overuse remains problematic, according to research presented at the American Society of Clinical Oncology annual meeting in Chicago.

Prostate Cancer

Overuse is more likely to be practiced by urologists who are in solo practice and those lacking a medical school affiliation and affecting older patients and those in ethnic minority groups, the authors found.

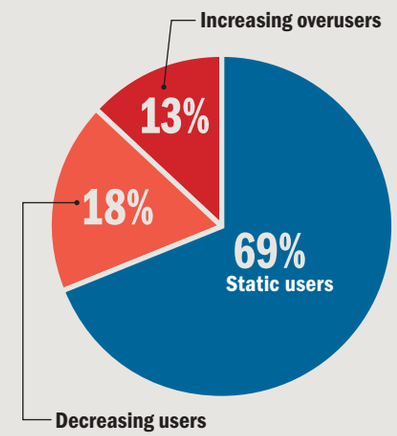
"About 25% of men with localized prostate cancer for whom ADT would not be recommended were still receiving GnRHa treatment in 2005. We were interested in trying to identify characteristics of the physicians involved as a first step towards addressing this problem," said first author Shellie D. Ellis, MA, PhD, a postdoctoral research fellow in health policy and management at the University of North Carolina, Chapel Hill.

"Clearly, limiting reimbursement did not uniformly alter practice patterns. Now, we will be trying to determine the reasons underlying persistent ADT overuse and the best ways to reach out to this large group of solo practitioners with information on ADT effectiveness and risks in order to improve quality of care," said Dr. Ellis, who worked on the study with Matthew E. Nielsen, MD, MS, Morris P. Weinberger, PhD, and colleagues.

The study included information for a nationwide group of 2,138 urologists treating nearly 13,000 men with early-stage and lower-grade prostate cancer diagnosed between 2000 and 2007. Characteristics of patients were extracted from Surveillance, Epidemiology, and End Results-Medicare data, and physician characteristics were identified through matching to American Medical Association physician data.

The analyses of physician overuse of ADT by study year led to the description of three groups of urologists based on patterns of prescribing before and after implementation of the Medicare Modernization Act. The majority (69%) were "static users" who had a low level of overuse in 2000 that remained relatively unchanged throughout the study period; 18% were "decreasing users" who demonstrated the highest level of overuse initially that remained steady until 2004, when it dropped precipitously and remained low; and 13% were "increasing overusers" whose overuse of ADT rose in 2004 and reached a level exceeding the highest users at the start of the study period.

UT Figure ADT prescription patterns



Source: Shellie D. Ellis, MA, PhD

Mixed effects regression modeling was performed to determine patient and provider characteristics associated with both initial overuse and increasing overuse over the study period. Provider variables analyzed included board certification, age, gender, years in practice, solo practice, medical school affiliation, percentage of minority patients, and whether the physician was U.S.-trained.

Time in practice not a factor

"We hypothesized that older physicians may have been less responsive to new evidence reporting on the harms associated with ADT and to reimbursement change, but that did not appear to be the case because time in practice was not associated with overuse," Dr. Ellis told *Urology Times*.

"Perhaps the reason why solo practitioners and urologists lacking any medical school affiliation were more likely to be overusers is that they are professionally isolated and possibly less likely to be involved in quality improvement activities, which are usually implemented through medical schools or various physician network or institutional groups."

Dr. Ellis noted that it was also concerning to find that the men most likely to be receiving inappropriate ADT represent vulnerable populations. Although it cannot be determined from the data whether these patients did not have access to appropriate intervention, analyses of the characteristics of patients treated by the increasing users showed they resided in communities with fewer resources and were less likely to receive radiation oncology consultations prior to treatment. UT

InBrief

FOR UP-TO-DATE NEWS, VISIT urologytimes.com/InBrief

FDA approves NDA for fast-acting PDE-5 inhibitor

The FDA has approved a supplemental new drug application for the phosphodiesterase-type-5 inhibitor avanafil (STENDRA).

Avanafil is now the only FDA-approved erectile dysfunction medication indicated to be taken as early as approximately 15 minutes before sexual activity, according to a press release from VIVUS, Inc. and Auxilium Pharmaceuticals, Inc. The previously approved prescribing information recommended administration approximately 30 minutes before sexual activity.

In clinical studies, when compared to placebo, avanafil helped more men achieve an erection in as early as approximately 15 minutes that lasted long enough to successfully complete sexual intercourse.

"ED patients in my practice are looking for a safe and effective treatment option that also works fast. In my opinion, STENDRA can be an appropriate and important treatment option because the clinical trial demonstrated that it provides a rapid onset of action in many men in as early as approximately 15 minutes," clinical trial primary investigator Wayne J.G. Hellstrom, MD, of Tulane University School of Medicine in New Orleans said in the release.

Data suggest racial disparity in high-risk PCa treatment

Health insurance coverage mitigates racial disparity, SEER data indicate

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

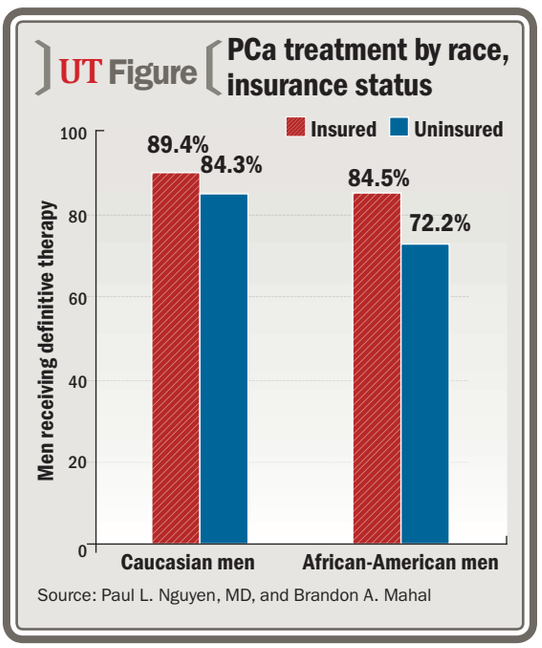
Boston—Results of a study analyzing data from the Surveillance, Epidemiology, and End Results (SEER) program add to evidence of race-related disparity in receipt of treatment for prostate cancer, but show that having health insurance reduces the difference in care.

Senior author Paul L. Nguyen, MD, told *Urology Times*, "Our findings suggest that expanding insurance coverage under the Affordable Care Act (ACA) may help reduce racial disparities in treatment patterns for high-risk prostate cancer, likely by increasing access to care.

"This would be particularly beneficial for African-American men with high-risk prostate cancer who are the most likely to face a poor prognosis, and most likely to be undertreated," added Dr. Nguyen, associate professor of radiation oncology at Harvard Medical School, Boston.

The study, which was presented at the American Society of Clinical Oncology annual meeting in Chicago and published online ahead of print in the *Journal of Geriatric Oncology* (May 23, 2014), included data from 64,277 men diagnosed with localized high-risk prostate cancer between 2007 and 2010. High-risk disease was defined as PSA >20.0 ng/mL, Gleason score ≥8, or clinical stage ≥T3a. Insurance status was dichotomized as uninsured or insured, regardless of insurance type.

Multivariable logistic regression analysis adjusting for a variety of sociodemographic features and known prostate cancer prognostic factors identified both race and insurance status as being significantly associated with receipt of definitive treatment ($p<.001$ for both). African-American men were 40% less likely than Caucasian men to receive definitive treatment, while men with insurance were 1.8-fold more likely to receive definitive treatment than their uninsured counterparts.



Insurance reduces disparity by 40%

Further analysis identified a statistical interaction between insurance status and race with respect to receipt of definitive treatment, such that having insurance reduced the racial disparity by about 40%. While African-American men were 62% less likely to receive definitive therapy than Caucasian men in the uninsured cohort, among men with insurance coverage, African-American men were only 38% less likely than Caucasian men to receive definitive therapy.

Lead author Brandon A. Mahal, a Harvard Medical School student, noted that additional analyses comparing men who were uninsured to those having either private insurance or Medicaid coverage found that Medicaid coverage also significantly reduced the racial disparity in receipt of treatment.

"This is an important finding because Medicaid is also being expanded under ACA," he said.

Mahal explained that the years 2007 to 2010 were analyzed because 2007 is the first year in which SEER began publishing information on insurance status and 2010 was the most recent year for which data were available.

"Future studies will be needed to assess the true impact of the ACA on racial disparity in treatment for prostate cancer. However, the first post-ACA information will not become available for analysis for another 4 to 5 years," Mahal said.

Discussing the limitations of the study, Mahal noted that the biggest issue is the lack of data on comorbidity in the SEER database.

"Without that information, we cannot rule out that some of the racial disparity found in our study might be due to different comorbidity rates within the different racial groups. However, in a sensitivity analysis, we used the rate of dying from causes other than prostate cancer as a means to evaluate how sick the patients were, and we found the same racial disparity in treatment receipt when we limited the analysis to patients having at least 3 years of follow-up after prostate cancer diagnosis," he told *Urology Times*. UT

DHEA levels may predict response to advanced PCa agent

Abiraterone shows modest clinical activity following ketoconazole treatment

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

San Francisco—Results of a phase II study from the Prostate Cancer Clinical Trials Consortium show that abiraterone acetate (ZYTIGA) has modest clinical activity in men with progressive metastatic castrate-resistant prostate cancer (mCRPC) previously treated with ketoconazole.

Perhaps more noteworthy, however, was the finding from an exploratory analysis indicating that men were unlikely to benefit from abiraterone if their plasma dihydroepiandrosterone (DHEA) level at treatment initiation measured by liquid chromatography/mass spectrometry (LC/MS) was below the assay's limit of quantitation, reported first author Won Kim, MD, at the American Society of Clinical Oncology annual meeting in Chicago.

"Abiraterone and ketoconazole may have overlapping mechanisms of resistance, but this has never previously been evaluated in a prospective clinical trial. The study shows that there are men who benefit from abiraterone despite prior CYP17 inhibition. Currently, however, that finding has limited clinical relevance since, at least in the United States, very few men with mCRPC will be started on ketoconazole," explained Dr. Kim, assistant clinical professor of medicine, division of hematology/oncology at the University of California, San Francisco.

"The finding associating baseline DHEA with response to abiraterone is of greater interest and merits further investigation, both

Please see **PCa AGENT,** page 12

Stable bladder neck in 70% of patients

MMC injections may end cycle of contracture Tx failures

Richard R. Kerr
GROUP CONTENT DIRECTOR

Burlington, MA—In patients with recurrent bladder neck contractures, history often repeats itself with multiple surgeries and poor outcomes, but reconstructive urologists are now hopeful they have a better solution.

Reconstruction

In a retrospective study, surgeons from the Lahey Clinic in Burlington, MA, reported that a novel approach using radial urethrotomy with mitomycin C (MMC) injections led to a patent bladder neck in 70% of patients after a single procedure and 81% after two procedures.

"For patients who have failed standard management of these challenging recurrent bladder neck contractures, they should be given the opportunity for this adjunctive agent to improve their outcome and need no further intervention," study co-author Jill C. Buckley, MD, told *Urology Times*.

"Otherwise, we would be just continuing to do what had been done—more incisions, more dilations, more Foley-dependent patients," said Dr. Buckley, a former Lahey Clinic faculty member who is currently associate professor of urology at the University of California, San Diego Health System.

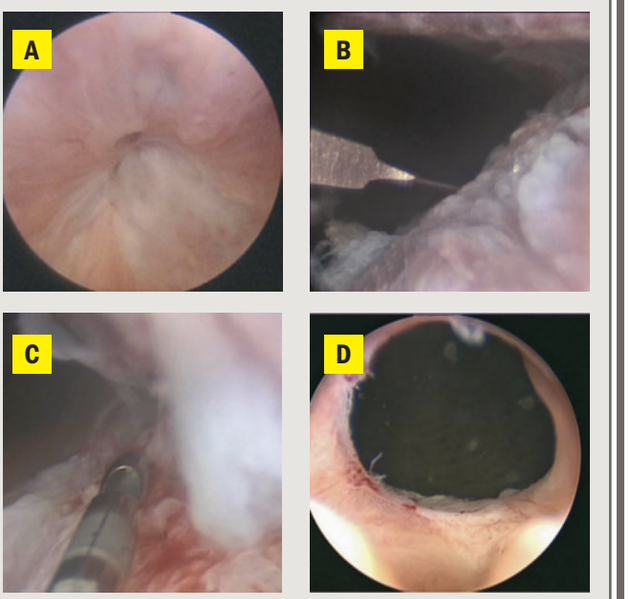
The study, presented at the AUA annual meeting in Orlando, FL, was designed to examine the long-term safety and efficacy of radial urethrotomy plus MMC in patients with recurrent bladder neck contractures.

A total of 37 patients were included, with a mean age of 64 years and a median contracture size of 10F. All patients had at least one prior failed direct vision internal urethrotomy (DVIU) or dilation. One-fourth of patients previously had two traditional endoscopic procedures, which included DVIU, dilation, or both; 16% had more than two procedures; one-third had indwelling catheters; and one-fourth were on a dilation schedule.

The surgical technique typically involves three to four incisions at the 10, 2, 4, and 8 o'clock positions. Using

Please see **MMC,** page 13

UT Figure



Bladder neck contracture shown preoperatively (A). Deep cold knife direct visual incision of the urethra is performed (B). Mitomycin C is injected into the groove of the incision (C). Cystoscopy at 12 months shows a widely patent and stable bladder neck (D).

Source: Photos adapted with permission from *J Urol* 2011; 186:156-60

PCa AGENT

continued from page 11

to determine the role of DHEA and other circulating androgens as a potential biomarker and for understanding mechanisms of abiraterone action and resistance."

The phase II study enrolled 42 men who were chemotherapy-naïve and had received ketoconazole for a minimum of 28 days. Other eligibility criteria required they have a testosterone level <50 ng/mL, normal baseline organ function, and a normal cortisol response to ACTH stimulation testing.

Men were treated with abiraterone, 1,000 mg daily, and prednisone, 5 mg twice daily until radiographic progression, which was defined as death, disease progression by RECIST or PCWG-2 criteria, or unequivocal clinical progression.

Baseline characteristics showed the men had used ketoconazole for a median of 43 weeks and had a median PSA of 48.5 ng/dL. Except for two men who stopped ketoconazole for Grade 3/4 toxicities, all others discontinued it because of prostate cancer progression.

Of 39 evaluable patients, 20 (51%) achieved the primary outcome endpoint of a ≥30% decline in PSA at 12 weeks, while 16 (41%) achieved a ≥50% decline at 12 weeks. Overall, radiographic progression-free survival (rPFS) for the group was 35.9 weeks. Median duration of ketoconazole treatment was significantly shorter among men who achieved the primary endpoint compared to those who did not (20 vs. 72 weeks, respectively).

Abiraterone was well tolerated, and its safety profile was similar to that seen in men without prior ketoconazole treatment.

DHEA levels linked to outcomes

Data from the LC/MS analysis showed baseline circulating DHEA levels were above the assay's limit of quantitation (LOQ) in 29 men and below the LOQ in eight men. Comparisons of outcomes between those two subgroups showed statistically significant differences that favored men with detectable DHEA for having a higher primary endpoint response rate (59% vs. 11%), longer median time to PSA progression (16 vs. 6 weeks), and longer rPFS (36.0 vs. 13.7 weeks).

One of Dr. Kim's co-authors has an employment or leadership position with and owns stock in Johnson & Johnson, and another co-author has received honoraria from Janssen Biotech. UT

UT Table

DHEA level and response to abiraterone

	Men with detectable DHEA	Men without detectable DHEA
Primary endpoint response rate	59%	11%
Median time to PSA progression	16 weeks	6 weeks
Radiographic progression-free survival	36 weeks	13.7 weeks

Source: Won Kim, MD

MMC

continued from page 12

a 21F scope, surgeons inject .3 to .4 mg per cc of MMC at these sites, and the bladder neck is subsequently calibrated to >26F.

Success was defined as a stable bladder neck >16F without the need for dilation or catheterization confirmed by passing a flexible cystoscope at 3, 6, 9, and 12 months.

"At a mean follow-up of 2 years, 70% of these patients had a stable bladder neck after one procedure. It increased to 81% after two procedures," said Kamal Nagpal, MD, a Lahey Clinic resident who presented the findings in Orlando.

Fourteen percent of patients required more than two procedures to maintain a stable bladder neck, and the failure rate was 5% (two patients). One-fifth of patients were incontinent after their procedure, and eight patients received an artificial urinary sphincter.

"To conclude, radial urethrotomy with mitomycin C is a safe, effective, and minimally invasive approach for these patients," Dr. Nagpal said.

Saline-controlled study needed

Audience member Allen F. Morey, MD, called the procedure a "very novel, interesting approach." But he questioned whether the outcomes were attributable to the mitomycin C or the depth of the transurethral incisions, citing his own group's study showing similar results in a similar patient series without the use of MMC (*Urology* 2013; 82:1430–5). "I would implore you to do a randomized, saline-controlled study," said Dr. Morey, professor of urology at the University of Texas Southwestern in Dallas.

"I am looking to attempt to get a blinded, randomized, controlled trial started to answer this question," Dr. Buckley said. "Funding is the issue. A recent study out of Michigan analyzed bladder neck incision alone versus bladder neck incision with MMC injection, showing a significant benefit to the adjunctive use of MMC. We are awaiting final publication."

Jeremy Myers, MD, assistant professor of surgery (urology) at the University of Utah, Salt Lake City, said a retrospective review of the procedure at several U.S. institutions uncovered three serious adverse events among 66 patients undergoing MMC injections in conjunction with bladder neck incisions. Two patients required cystectomy as a result of complications.

Dr. Buckley noted that her group uses MMC judiciously, adhering to a concentration dose that's well described in the literature, and is careful not to over instill the medication in one setting.

"We have not experienced local wound breakdown, ulceration, or delayed healing and believe this is due to a strict adherence to our predetermined incision and dosage technique," she said. "It is a powerful agent that we know can be effective, but increasing the dose or amount delivered also increases the risk of toxicity and thus the potential for short- or long-term complications." UT

UT EXCLUSIVE VIDEO

bitly.com/MMC-injections
Dr. Buckley demonstrates the use of radial urethrotomy plus **mitomycin C** injections in patients with recurrent contractures.

Oncofertility: Current practice and vision for the future

In male patients, semen cryopreservation is just one way to 'minimize the cost of cure'

Ahmed A. Hussein, MD James F. Smith, MD, MS

Dr. Hussein

Dr. Smith

Dr. Hussein is assistant lecturer of urology at Cairo University, Cairo, Egypt, and **Dr. Smith** is director of male reproductive health and assistant professor of urology; obstetrics, gynecology, and reproductive sciences; and health policy at the University of California, San Francisco.

The number of cancer survivors has grown over the past several decades as a result of advances in diagnosis and treatment. Cure and survival remain each patient's top priority, but improved survival has spurred greater interest in quality of life after treatment. Comprehensive cancer care for male patients should aim at "minimizing the cost of cure" and maintaining their overall well-being, including their ability to father children. Unfortunately, many may not be able to have children due to the effects of cancer and its treatment.

In this article, we examine the effect of malignancy and anti-cancer treatment on fertility, review current fertility preservation methods, and offer a preview of fertility preservation techniques that hold future promise.

How can cancer affect fertility?

Many types of cancer are associated with impaired semen parameters and infertility. Pain and constitutional manifestations have been associated with impaired semen parameters. Prior to initiation of any treatment, patients with Hodgkin's disease, testicular cancer, and extragonadal germ cell tumors have impaired semen quality (*Ann Oncol* 2001; 12:1307-11).

Anticancer treatment can cause persistent or long-lasting damage to the testis. The extent of damage varies with the cancer type, patient age, and type and dosage of the treatment modality (table 1). Typical cytotoxic therapy disrupts spermatogenesis by targeting rapidly dividing spermatogonial stem cells.

Radiotherapy. Direct irradiation of the testicles, as in cases of leukemic infiltration of the testes or as part of whole-body irradiation prior to bone marrow transplantation, causes direct damage of the testis. Cranial irradiation of brain tumors may cause disruption of the hypothalamic-pituitary-gonadal axis and endocrine failure. This side effect can occur with doses as low as 1.2 Gy, and irreversible damage occurs with doses of 4 Gy or more. It is worth mentioning that Leydig cell function (ie, testosterone production) is usually maintained for doses up to 20 Gy (*J Endocrinol* 1989; 120:161-5). Therefore, infertility secondary to oligospermia or azoospermia can occur despite normal development of secondary sexual characteristics.

Chemotherapy. Similar to radiotherapy, gonadotoxic chemotherapy affects mainly the germ cells, causing oligospermia or azoospermia, with hypogonadism a less frequent consequence. Alkylating agents such as cyclophosphamide and busulfan carry the highest risk of infertility (table 2). In addition, most chemotherapy regi-

UT Table 1 How anticancer treatments affect fertility

Treatment	Effect on fertility
Irradiation of testicles	Direct damage to the testis. Dose and location dependent
Cranial irradiation	May disrupt the hypothalamic-pituitary-gonadal axis and cause endocrine failure
Gonadotoxic chemotherapy	Affects germ cells, causing oligospermia or azoospermia; hypogonadism is less frequent
Tyrosine kinase inhibitors	Not currently established
Retroperitoneal surgeries	May injure nerves responsible for ejaculation or seminal emission, causing retrograde ejaculation or anejaculation
Bone marrow and stem cell transplant	Gonadotoxic therapies have been shown to result in infertility in majority of patients receiving bone marrow and stem cell transplant

Source: Ahmed A. Hussein, MD, and James F. Smith, MD, MS

Series Editor

Christopher M. Gonzalez, MD, MBA, is professor of urology at Northwestern University's Feinberg School of Medicine, Chicago.

mens involve the use of a combination of agents, which may have a synergistic detrimental effect on fertility. The risk posed by targeted therapies, such as tyrosine kinase inhibitors, to male fertility and pregnancy outcome is yet to be established. Patients should be counseled about the risks of infertility and consider pre-treatment sperm cryopreservation.

Surgery. Retroperitoneal surgeries, such as retroperitoneal lymph node dissection or resection of retroperitoneal tumors, may injure nerves responsible for ejaculation or seminal emission, causing retrograde ejaculation or anejaculation.

Bone marrow and stem cell transplant. Bone marrow and stem cell transplantation are necessary therapies for many malignant and benign conditions. Worldwide, more than 50,000 procedures are performed annually, with more than half of the patients in their reproductive age. An integral part of the procedure is to use "induction" chemotherapy and/or radiation therapy and then replace it with highly specialized stem cells that develop into healthy bone marrow. These gonadotoxic therapies (eg, pelvic irradiation or alkylating agents such as cyclophosphamide and busulfan) resulted in infertility in more than two-thirds of pediatric patients who had received allogeneic stem cell transplant in one study (*Bone Marrow Transplant* 2012; 47:271-6).

UT Table 2

Cytotoxic chemotherapy stratified by risk of gonadotoxicity

Lower risk	Intermediate risk	Higher risk
Bleomycin	Carboplatin	Busulfan
Dactinomycin	Cisplatin	Chlorambucil
Mercaptopurine	Doxorubicin	Chlormethine
Methotrexate		Cyclophosphamide
Vinblastine		Ifosfamide
Vincristine		Melphalan
		Procarbazine

Source: Ahmed A. Hussein, MD, and James F. Smith, MD, MS

Methods of fertility preservation

Semen cryopreservation is a well-established fertility preservation method for sexually and reproductively mature males. Prompt referral to a fertility specialist and banking as many samples as possible prior to treatment is crucial. The quality and number of healthy cryopreserved sperm determines the future reproductive options available to each patient. Advancements in semen cryopreservation in conjunction with in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) have revolutionized fertility options for subfertile patients.

Other options have been proposed to protect against the effects of radiotherapy, including fractionation of the radiation dose, shielding the testicles during radiotherapy, and surgical relocation of the gonads away from the radiated field. Alterations in the chemotherapy protocols have been also proposed. However, the effectiveness of these methods remains questionable (*Pediatrics* 2008; 121:e1461-9).

The role of oncologists and other providers

The medical oncology team should emphasize the possible fertility consequences of the anticancer treatment. Oncologists appropriately focus on cancer survival and generally select treatment with the highest survival outcome. However, this should be done in the context of comprehensive patient care and minimizing early and late adverse effects, including infertility.

Physicians and other providers should address infertility as a possible consequence for cancer treatment, counsel them about fertility preservation strategies, and promptly refer them to a fertility specialist if needed. The American Society of Clinical Oncology has recommended that all patients facing sterilizing therapy should be advised of these risks. Patients should be referred as early as possible for sperm cryopreservation during the small window between diagnosis and initiation of treatment. Men with poor sperm quality on these initial semen samples should be rapidly referred to and seen by a reproductive urologist to discuss pre-treatment fertility preservation strategies. Establishing a network between fertility specialists and practitioners dealing with cancer patients, with prompt referral of patients during the window after diagnosis and prior to receiving cytotoxic therapy, would maximize the patients' fertility preservation chances (*J Clin Oncol* 2013; 31:2500-10).

Obstacles to fertility preservation

Awareness of fertility preservation. Following their cancer diagnosis, patients are usually overwhelmed by the cancer diagnosis and prognosis, and may not be aware of or initially concerned about the possible effects on their fertility. Moreover, many may not be aware of the possibility of fertility preservation, or think it may cause a delay in cancer treatment and therefore worsen prognosis. Health care providers should provide clear information about these risks, the fact that fertility preservation rarely delays cancer treatment, and promptly refer patients for fertility preservation.

Cost. The estimated cost of preserving three semen samples for 3 years has been estimated at approximately $1,500 (U.S.). Further, the utilization of this sperm may require IVF/ICSI, an approach that can cost a patient over $20,000 (*J Urol* 2014; 191:427-32). For many, failure of insurance to cover fertility preservation makes these services inaccessible. Health care providers should encourage patients to explore their coverage and advocacy programs to identify financial assistance. Many sperm banks facilitate the process of payment by offering monthly payment plans, which may make it more affordable (*J Clin Oncol* 2013; 31:2500-10).

On the other hand, under the Affordable Care Act, infertility services are not included among the list of Essential Health Benefits. Moreover, it includes some guidelines that may inhibit couples from seeking fertility treatment. Currently, the Internal Revenue Service tax code considers storage of sperm and IVF as non-reimbursable medical expenses. The new tax code will allow deductions for fertility treatments of more than 10% of patients' income rather than 7.5%, resulting in a significant reduction of the amount a couple can claim.

Future fertility preservation options

Many promising investigational methods for fertility preservation are in development, particularly for prepubertal boys facing sterilizing cancer treatment. In the two most promising methods, a testicular biopsy is obtained and cryopreserved prior to cancer therapy. Thawed testicular tissue could be used either for in vitro maturation of sperm cells or cells could be transplanted back to the patient after successful cancer treatment. Mouse models have demonstrated the potential for success of using neonatal testicular tissue differentiated in vitro to mature sperm and used for IVF/ICSI (*Nature* 2011; 471:504-7). Animal models have successfully demonstrated the feasibility of autologous spermatogonial stem cell transplantation, which utilizes thawed testicular tissue reintroduced to the patient's testicles after cure (*Cell Stem Cell* 2012; 11:715-26, *Biol Reprod* 2009; 81:898-905).

Conclusion

Dramatic improvement in survival after cancer therapy has spurred much interest in post-treatment quality of life for male cancer patients, including their ability to father children. Semen cryopreservation is a well-established method of fertility preservation in men treated with potentially sterilizing cancer therapy. Although promising fertility preservation approaches for prepubertal boys are under investigation, many hurdles remain before they can be offered widely.

Educating patients about the risks of infertility after cancer treatment and referring them for fertility preservation should be done early after diagnosis in men at risk for impaired fertility. Establishing a link between fertility specialists and physicians treating cancer patients is crucial to provide these services effectively. UT

Xtandi® (enzalutamide) 40 mg capsules

NEW INDICATION

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

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

Warnings and Precautions In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of patients who were treated with XTANDI and 0% treated with placebo. In Study 2, conducted in patients with chemotherapy-naïve metastatic CRPC, seizure occurred in 0.1% of patients who were treated with XTANDI and 0.1% treated with placebo. Patients experiencing a seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced a seizure, and limited clinical trial experience in patients with predisposing factors for seizure. Study 1 excluded the use of concomitant medications that may lower threshold, whereas Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity during which sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Adverse Reactions The most common adverse reactions (≥ 10%) reported from the two combined clinical trials that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Other Adverse Reactions include:

- Laboratory Abnormalities: In the two studies, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).
- Infections: In Study 1, 1% of XTANDI versus 0.3% of placebo patients and in Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Significantly extended radiographic progression-free survival*†[1]

- 83% reduction in risk of radiographic disease progression or death with XTANDI + GnRH therapy* vs placebo + GnRH therapy* (co-primary endpoint: HR = 0.17 [95% CI, 0.14-0.21]; *P* < 0.0001)
- Estimated median radiographic progression-free survival was not reached (95% CI, 13.8-not reached) for XTANDI + GnRH therapy* and was 3.7 months (95% CI, 3.6-4.6) for placebo + GnRH therapy*[1]

Significantly delayed time to chemotherapy initiation*†[1]

- Delayed time to chemotherapy initiation by a median of 28.0 months with XTANDI + GnRH therapy* vs 10.8 months with placebo + GnRH therapy* (HR = 0.35 [95% CI, 0.30-0.40]; *P* < 0.0001)

Significantly improved overall survival*†[1]

- 29% reduction in risk of death with XTANDI + GnRH therapy* vs placebo + GnRH therapy* (co-primary endpoint: HR = 0.71 [95% CI, 0.60-0.84]; *P* < 0.0001)
- Estimated median overall survival was 32.4 months (95% CI, 30.1-not reached) for XTANDI + GnRH therapy* and 30.2 months (95% CI, 28.0-not reached) for placebo + GnRH therapy*[1]

Oral, once-daily dosing with no required steroid coadministration[1]

- Dosage: XTANDI 160 mg (four 40 mg capsules) is administered orally, once daily
- Steroids were allowed but not required‡

Visit XtandiHCP.com or snap the QR code for more information

- Falls: In the two studies, falls including fall-related injuries occurred in 9% of XTANDI patients vs 4% treated with 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.
- Hypertension: In the two studies, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of XTANDI or placebo treated patients.

Drug Interactions

- Effect of Other Drugs on XTANDI - Administration of strong CYP2C8 inhibitors can increase the plasma exposure to XTANDI. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI cannot be avoided, reduce the dose of XTANDI. Co-administration of XTANDI with strong or moderate CYP3A4 and CYP2C8 inducers may 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 co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

†As seen in the PREVAIL trial (Study 2): a multinational, double-blind, randomized, phase 3 trial that enrolled 1717 patients with metastatic CRPC that progressed on GnRH therapy or after bilateral orchiectomy, and who had not received prior cytotoxic chemotherapy. All patients continued on GnRH therapy.[1,2]

‡In the PREVAIL trial, 27% of patients in the XTANDI arm and 30% of patients in the placebo arm received glucocorticoids for varying reasons. In the AFFIRM trial (Study 1), 48% of patients in the XTANDI arm and 46% of patients in the placebo arm received glucocorticoids. AFFIRM was a phase 3, multicenter, placebo-controlled, randomized trial that enrolled 1199 patients with metastatic CRPC who had previously received docetaxel.[1]

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424-433.

astellas MEDIVATION

Xtandi® (enzalutamide) 40 mg capsules

Xtandi® (enzalutamide) 40 mg 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 (CRPC).

CONTRAINDICATIONS

Pregnancy XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. 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 (8.1)]*.

WARNINGS AND PRECAUTIONS

Seizure In Study 1, which enrolled patients who previously received docetaxel, 7 of 800 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In Study 2, 1 of 871 (0.1%) chemotherapy-naive patients treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizure.

Limited safety data are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. 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, and brain arteriovenous malformation. Study 1 excluded the use of concomitant medications that may lower the seizure threshold, whereas Study 2 permitted the use of these medications.

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. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

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.

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchiectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids.

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

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 Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in Study 1

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	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
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[c]	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[d]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[e]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[f]	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

Table 1. Adverse Reactions in Study 1 (cont.)

Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a CTCAE v4
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
f Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer Study 2 enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in Study 2

	XTANDI N = 871		Placebo N = 844	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	46.9	3.4	33.0	2.8
Peripheral Edema	11.5	0.2	8.2	0.4
Musculoskeletal And Connective Tissue Disorders				
Back Pain	28.6	2.5	22.4	3.0
Arthralgia	21.4	1.6	16.1	1.1
Gastrointestinal Disorders				
Constipation	23.2	0.7	17.3	0.4
Diarrhea	16.8	0.3	14.3	0.4
Vascular Disorders				
Hot Flush	18.0	0.1	7.8	0.0
Hypertension	14.2	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[c]	11.3	0.3	7.1	0.0
Headache	11.0	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[d]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[e]	11.0	0.6	8.5	0.6
Infections And Infestations				
Upper Respiratory Tract Infection[f]	16.4	0.0	10.5	0.0
Lower Respiratory Tract And Lung Infection[g]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0

Table 2. Adverse Reactions in Study 2 (cont.)

Renal And Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning And Procedural Complications				
Fall	12.7	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	18.9	0.3	16.4	0.7
Investigations				
Weight Decreased	12.4	0.8	8.5	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0.0	1.4	0.0

a CTCAE v4
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes dyspnea, exertional dyspnea, and dyspnea at rest.
f Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
g Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Laboratory Abnormalities In the two randomized clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients treated with placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

Infections In Study 1, 1% of patients treated with XTANDI compared to 0.3% of patients treated with placebo died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls and Fall-related Injuries In the two randomized clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with 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.

Hypertension In the two randomized trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

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 by 2.2-fold 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 (12.3)]*.

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 (12.3)]*.

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 (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category X *[see Contraindications (4)]*.

Risk Summary

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no human 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. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. 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.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

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 1671 patients who received XTANDI in the two randomized clinical trials, 75% were 65 and over, while 31% 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 CRPC 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 (12.3)]*.

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 (12.3)]*.

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 seizure following an overdose.

NONCLINICAL TOXICOLOGY

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-, 13-, and 39-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).

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

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

Revised: September 2014

14B006-XTA-BRFS

Rx Only

astellas MEDIVATION

076-0472-PM

Q&A

IAN THOMPSON, MD

Dr. Thompson was interviewed by *Urology Times* Editorial Consultant J. Brantley Thrasher, MD, professor and chair of urology at the University of Kansas Medical Center, Kansas City.

LOW-RISK PROSTATE CANCER

Low-risk PCa: Patients *can* make an informed decision

Low-risk prostate cancer raises a number of questions about current screening, diagnostic, and treatment practices. In this interview, Ian Thompson, MD, answers questions about the downside of diagnosing low-risk disease, the burdens of active surveillance and how to minimize them, and how his own approach to screening and biopsy have changed. Dr. Thompson is professor of urology at the University of Texas Health Science Center, San Antonio and director of the Cancer Therapy and Research Center.

Q: ***We want you to address some of the issues we face with low-risk prostate cancer. We have been challenged to a great degree with questions about whether we are screening too many patients with PSA, what to do about low-risk prostate cancer, and whether we should actually stop calling low-risk disease "cancer." What do you think?***

A: The challenges that we face with low-risk prostate cancer are not unique to prostate cancer. We published a paper in *Lancet Oncology* in May (2014; 15:e234-42) that showed very clearly that this is a problem across all cancers. The question of "Should we call it cancer?" is an issue not only for urologists, but also those who treat thyroid cancer, melanoma, lung cancer, breast cancer, and others.

It's a little more of an issue for urologists because we have the PSA test and biopsies, and now we know unequivocally that the cancers we tend to find through screening—the ones that we increase the detection of—disproportionately tend to be such low risk that we know with a pretty high degree of certainty that many of them will never impact the patient's life expectancy. That's why the U.S. Preventive Services Task Force, for example, recommended against PSA testing. When these low-risk cancers are included in the group of men that you diagnose and if you treat them all, this unfortunately creates a greater harm than the benefit from detecting the high-risk cancers and treating them with multimodal therapy. That is why this is such a big issue that we really need to address.

What's the downside of diagnosing these very low-risk cancers?
J. BRANTLEY THRASHER, MD

There is a huge downside, and I would contend that there are actually several forks in the road. The first fork in the road is, do you do a PSA?
IAN THOMPSON, MD

Q: ***Many urologists, myself included, see this as two separate forks in the road. Getting a PSA test is different from what we do with the information we obtain from it. What's the downside of diagnosing these very low-risk cancers?***

A: There is a huge downside, and I would contend that there are actually several forks in the road. The first fork in the road is, do you do a PSA? The AUA guidelines are very clear that if you are less than 40 years old, you probably don't benefit. If you are 40 to 55 years old and low risk, the likelihood of benefit is quite low because in younger men, you are more likely to find low-grade, low-volume disease that rarely causes a problem. There are ways that you can actually predict who's at greater likelihood of low-risk disease: men with lower PSAs, those whose PSA went up to a small degree, are very young and Caucasian, and whose rectal exam is normal. Those people preponderantly have low-risk disease.

The second fork in the road, I would contend, is also a problem. That is when your patient is found to have low-risk disease, thinks about it, and says, "I'm going to go on active surveillance." Active surveillance is not a good thing. Patients choose it because they prefer the quality of life outcomes rather than those for radiotherapy or surgery, but active surveillance is a bad outcome. Patients repeatedly want to know their PSA results, even when they were just tested a week ago. They are still anxious. They have repetitive biopsies, sepsis, and so forth.

Q: ***I've heard it said jokingly that PSA stands for "patient-stimulated anxiety," and aside from anxiety, there are other risks of proceeding to transrectal ultrasound biopsy, including fluoroquinolone-resistant infection. You have a great calculator on your website that helps patients and physicians make these kinds of decisions. Tell us about that.***

A: I use it all the time for that first fork in the road. The first fork occurs with the man who whose dad had prostate cancer, is Caucasian, young, and his PSA was previously 1.0 ng/dL. Now it's 1.5 ng/dL. He asks if he should come in for a biopsy. The problem with those circumstances is that that man may have a 2% risk of a high-grade tumor, but he may have a 15% risk of a low-risk tumor. Out of a hundred men, there may be a two in a hundred chance that you might help that man, but there's a 15 in a hundred chance—15 times greater likelihood—that you might find an indolent tumor and, by doing a biopsy, a 2% to 4% risk of sepsis.

When you present those data to him, he may say, "Maybe I don't want a biopsy now. Maybe we should wait, repeat the PSA in 6 months or a year, and make a deferred decision." You can also use that approach for the second fork in the road: treatment versus no

treatment at the time of active surveillance decision making.

The online risk calculator, based on data from the Prostate Cancer Prevention Trial (PCPT), helps determine a man's risk of low-grade and high-grade prostate cancer. Originally the results were just presented as percentages. The results are now also presented graphically with "emojis," which are pictures of faces that illustrate good outcomes, bad outcomes, and the outcomes in between.

What do you tell patients when they reach age 75, and when do you feel comfortable turning these patients loose?
J. BRANTLEY THRASHER, MD

Oftentimes the patient tells you what they want to do, and that's my preference. You can't be 100%.
IAN THOMPSON, MD

The risk calculator is free and is constantly being improved. I use it in virtually every patient. It helps me help my patient make an informed decision. To find it, Google, "prostate cancer risk calculator," and click on the top result that's not an advertisement.

Q: ***Some European urologists are getting away from transrectal biopsies and going back to transperineal biopsies to avoid infectious complications. There have also been recent papers about the use of rectal swabs. How do you perform prostate biopsies in your clinic? Also, what are the other burdens of active surveillance?***

A: This is one of the reasons we're thinking about ways that you can unburden active surveillance. My standard approach, which is the approach used in the Canary Foundation's prostate cancer active surveillance study, is PSAs quarterly, exams every 6 months, and biopsies every 2 years. I generally don't do a first biopsy within 6 months or so, as long as I've had the pathology read and as long as it's had an adequate number of cores. I may do it if the patient has something that doesn't make sense, such as higher volume disease or possibly some component of Gleason 4 disease. Generally that's what we do, but that's a tremendous burden for the patient.

Regarding my approach to biopsies, I'm still doing a dozen cores transrectally. In patients who've had a prior biopsy, I also give them gentamicin. Now, I always ask myself if that is the right thing to do because it's increasing pressure on the flora of the gut. But I saw an increasing number of patients who developed fevers and chills just on the fluoroquinolone, and I found that that substantially decreased. When a patient develops sepsis from a biopsy for active surveillance, that automatically takes away a huge amount of benefit that you've provided.

The other thing I am doing is reducing the frequency of biopsy in some patients. For example, in the patient with microfocal Gleason 3/3 disease that started in his early 60s, who's now in his early 70s and has had two negative biopsies, I'm spreading it out more. We're working with the Canary Foundation on developing a risk-assessment tool to be able to predict the person who's at a low likelihood of coming off active surveillance, so you would be able to tell a patient there's a 95% or 96% likelihood that your biopsy won't find something that will take you off surveillance.

Q: ***Does your follow-up of patients on active surveillance change if the patient has multiple biopsies because, as you know, performing multiple biopsies increases the risk of complications?***

A: It's important to point out that I have been taught as much about prostate cancer by our research as by our patients. I've had a number of patients who said they don't want another biopsy and pointed out that their PSA and exam have been normal, and nothing has been found on three biopsies. They are some pretty smart folks. They say, "If that were a problem, you'd likely find it in this circumstance, and you haven't, which means that I probably have a lower risk of high-grade disease than the guy on the street with a PSA of 1, so why are you repeating my biopsy?"

Q: ***Do you feel there is any form of imaging that should be used now to help guide urologists, or are they all still experimental?***

A: I think there are some circumstances where it may be helpful, for example, in the man whose PSA or rectal exam or biopsy are not in agreement with each other. One example is a man who went on a 5-alpha-reductase inhibitor, his PSA went down, it starts to go back up, and your repeat biopsy doesn't find anything.

Please see **LOW-RISK PCa,** page 22

LOW-RISK PCA

continued from page 21

Another example is the man whose PSA is rising and whose subsequent biopsy doesn't find anything. Particularly if that man is younger, I worry, and I'll order a 3T MRI with a coil. I'm not sure the coil is absolutely necessary, but there's no question that a multiparametric MRI with a 3T yields much better images. If I don't see anything, I don't do anything.

My problem with this, however, is that the moment you do this, people will say, "If it worked for one guy, let's apply it to everyone." Then the problem comes in that the specificity of MRI in most series is about 60% to 80%, averaging around 70%. Once you take a technology that has a 70% specificity and apply it to a population whose prior probability of disease is very low, 30% of them will be false positive. Then what are you going to do? Are you going to do targeted biopsies in those men and take more cores? You are applying all of that additional burden and cost associated with repeating the biopsies on people who have very low risk to begin with. I am concerned that if we apply it in a fashion that is not individualized, there will be a net harm.

Q: ***At what point do you add a saturation biopsy or a template biopsy? There are urologists doing as many as 70 cores. Is there ever a place for that?***

A: I will do perhaps one or two or three a year. It's very unusual. In general, I prefer to do the MR and if there is a lesion on the MR, if I've done an adequate number of biopsies elsewhere, I'll just target the lesion. Sometimes they'll be positive and there will be bulky high-grade disease, but there are also false positives as well.

Again, it really needs to be individualized. I think saturation biopsies tend to be a last-ditch resort. I don't do it perineally, and I think you can do it adequately transrectally, except perhaps in the largest of glands. The difficulty from a technical standpoint is that if you push the needle way into the prostate and then fire it, it often doesn't get a throw. We push the needle way in, pull back about a centimeter, and then hit a throw, which provides the momentum to obtain an adequate biopsy. In general, if the MR is negative, the likelihood that there's a high-grade tumor there is really low. The negative predictive value is 90% to 95%.

Q: ***Are there biomarkers that you're excited about that may help us prevent biopsy in patients who don't need it or help determine patients who do need it?***

A: There are some tissue-based tests—the Oncotype DX test from Genomic Health and the Prolaris test from Myriad—that can be used to predict tumor grade or recurrence. PCA3 and ProPSA are also available, and percent-free PSA, fascinatingly is pretty inexpensive and is one of the most powerful biomarkers to indicate the presence/absence of cancer. T2ERG may be something that's useful, and there's a host of other analyses, such as urinary-based methylation studies, that are coming into play.

A more recent, fascinating one that Elizabeth Platz and Angelo De Marzo looked at in the PCPT sample is something very cheap: presence of inflammation in the benign part of the prostate. In patients with low PSA levels, they've shown it has an odds ratio of four, meaning inflammation elsewhere in the prostate increases the likelihood fourfold that there's high-grade cancer present.

How has your approach to PSA screening changed?

J. BRANTLEY THRASHER, MD

I think the thing that I'm better at doing now is identifying the man who's most likely to benefit.

IAN THOMPSON, MD

Currently, I think you can use the PCA3, and you can use one of the tissue-based tests. You might also use the presence of significant inflammation in biopsy cores to make a recommendation. But it needs to be done appropriately.

When you use predictive markers in a very low-risk population, your likelihood of a false-positive result is far greater than a true positive. It really needs to be limited to the patient in whom something—his PSA, exam, his risk factors, or biopsy—doesn't feel right.

There are actually statistical ways that can be developed. We're working with Rice University, for example, to develop a chip-based approach that looks at a broad range of markers and then adds additional markers based upon what's called the likelihood ratio. You can use artificial intelligence to put several risk factors together and then make a recommendation on when to use markers. You don't want to use additional markers in people who have very low-risk disease. The other way of looking at additional markers is that they are probably a bad idea in people who de novo have very high-risk disease as well, as they could give you a false sense of security that you don't need to treat them.

Q: ***In this country, there are obvious concerns about medical litigation and what you can and can't tell patients. What do you tell patients when they reach age 75, and when do you feel comfortable turning these patients loose?***

A: Oftentimes the patient tells you what they want to do, and that's my preference. You can't be 100%. A good example is an 80-year-old patient who was followed by his primary care physician, and had very low PSA levels over a long period of time. When he turned 80, everyone was in agreement that he probably no longer needed PSAs; 2 years later, his PSA was in the 400 range. So you can never be 100%, and the patient needs to understand that.

But for the man whose PSA is stable and biopsies don't show much of anything, the utility of continuing the PSA long-term is very, very low. If you think about it, most people who die of prostate cancer have high-grade disease at the time of the original biopsy. The paradox is that, when you sit down for the first time with a man with low-grade disease, you can tell him he has a lower likelihood of dying from prostate cancer than the man in the general population who doesn't have it. Once they begin to understand that, they'll tell you what they want to do.

Q: ***In your practice, with all the studies you've done, how has your approach to PSA screening changed?***

A: I think the thing that I'm better at doing now is identifying the man who's most likely to benefit. Consider a 45- or 50-year-old man who walks in with some voiding symptoms, and I start him on tamsulosin. Historically, we would tell him to get his PSA checked on the way out.

Now, the conversation isn't too long but goes something like this: There's a blood test and there are pros and cons of it. The advantage is that if you have prostate cancer, there's a greater likelihood we'll find it. The disadvantage is that we may find tumors that are inconsequential, and treatment of those inconsequential tumors can lead to side effects. I ask them if they've ever had a PSA test, if they would like to have one, or if they'd like to learn more.

That short conversation is now part of my practice. I make sure that the patient understands he is not just being offered a blood test, but he is embarking on a journey. Some people may say they absolutely want a screening test because their neighbor died of prostate cancer. Others might say, "You mean, if I get a test that finds a tumor that might not be consequential, and the treatment for that inconsequential cancer might render me impotent? I'm not interested." And then there are people in between, and you can provide them more information to help them make a decision.

Q: ***I find that what patients are looking for***

is direction. I don't find many people who don't have some bias, but they generally ask me as the expert, "What should I do?"

A: I would respectfully disagree. I find the number of people who turn everything over to me is really low. Look at the newly married person, for example. He and his spouse are concerned about longevity, and sexual function is really important, so the potential detection of an inconsequential cancer that can lead to sexual dysfunction is a real issue. In the man who is no longer is sexually active, it's completely different.

You can pick up in the conversation with the patient and often the spouse how much information they want. You can help them make the decision, but I'm uncomfortable sending that low-risk man for a PSA without at least telling him that there are some risks and benefits. I find that patients may be initially uncomfortable with me helping them make a decision but ultimately truly appreciate it.

In a man who's 60, are you even bringing up the discussion of PSA screening?
J. BRANTLEY THRASHER, MD

Absolutely. The AUA guidelines state that men who are 55 to 70 should have informed decision making.
IAN THOMPSON, MD

Q: ***In a man who's 60, are you even bringing up the discussion of PSA screening?***

A: Absolutely. The AUA guidelines state that men who are 55 to 70 should have informed decision making. I cannot ignore the evidence of the fall in mortality—and some of that benefit may be due to improved treatment—there's incontrovertible evidence that screening makes a difference. To not tell that patient those results is unjust. Outside that age group—the younger man or the older man—there are some other risks that they need to understand.

Q: ***Do you have anything else that you would like to add?***

A: First, I suggest again the use of the online risk calculator and tell patients about it. Second, when a patient is referred to you who's had a low PSA before and has a spike in their PSA, repeat it. PSA has a high degree of variability. Can you imagine going to an internist who finds your blood pressure is a little high and immediately puts you on an antihypertensive? Repeat the PSA, and you will look like a genius. UT

UT EXCLUSIVE VIDEO

bitly.com/Thompson-Q&A

Watch our video highlights of Dr. Thrasher's interview with Dr. Thompson online.

Oral testosterone agent outperforms gel in hypogonadism study

Repros Therapeutics Inc. said its investigational oral testosterone formulation (Androxal) exhibited superiority to a leading FDA-approved topical gel (Androgel 1.62) and placebo in the first of two identical studies. Androxal was found superior in the two co-primary endpoints: percent change from baseline in average sperm concentration and percent of subjects considered to be responders. A responder is defined as an individual achieving a 24-hour average testosterone in the normal range with associated average sperm concentration >10 million/mL. Multiple secondary endpoints also showed statistically significant differences between the Androxal and gel groups. These include: change in LH and FSH, percent of subjects who become severely oligospermic, induction of hormone dependence via assessment of morning testosterone levels comparing baseline to 1 week after the end of dosing, and impact on testicular size at the end of the dosing period.

Multiple sites study vaccine-based treatment for mCRPC

A placebo-controlled clinical trial being conducted at several worldwide sites is examining Bavarian Nordic's investigational vaccine-based treatment PROSTVAC in patients with metastatic, castration-resistant prostate cancer. The goal of the immunotherapy study is to determine if PROSTVAC improves survival when combined with a drug that helps boost the body's ability to fight infection, according to Rutgers Cancer Institute of New Jersey, one of the trial sites. Results from a previous clinical trial at the Cancer Institute of New Jersey that examined two forms of PROSTVAC gave researchers information on the safety of using this investigational drug (*J Transl Med,* Jan. 3, 2006). The new study will further examine how well PROSTVAC does in improving survival outcome in patients with metastatic prostate cancer. PROSTVAC-V is derived from a vaccinia virus that was used for many years to vaccinate against smallpox. PROSTVAC-F is made from the fowlpox virus, which is found in birds and not known to cause any human disease.

Enrollment completed for trial of steam-based BPH treatment

NxThera has completed enrollement in its Rezum II IDE clinical trial for the treatment of BPH. The trial evaluated use of the Rezum system to treat obstructive prostate tissue by convectively delivering sterile water vapor, or steam, directly into the prostate in a minimally invasive procedure that can be performed in a matter of minutes, NxThera said. The U.S. multicenter study enrolled 195 men age 50 years or older, who were randomized 2:1 to treatment with the Rezum system versus a control procedure.

Patient enrollment begins on balloon system for SUI

Solace Therapeutics, Inc. has begun patient enrollment in a clinical trial to assess the safety and effectiveness of the Solace Bladder Control Balloon System in women who experience urine leakage during times of physical movement. Known as SUCCESS (Stress Urinary InContinence Control Efficacy and Safety Study), the randomized, multicenter, controlled trial is anticipated to enroll 220 women at up to 20 clinical sites across the United States. The study endpoints evaluate women's improvement in quality of life and reduction in urine leakage. The SUCCESS trial is Solace Therapeutics' third randomized, controlled study to evaluate this treatment option.

Immune response linked with survival in PCa vaccine study

Generex Biotechnology Corp. announced publication of a follow-up study from a phase I clinical trial of the immunotherapeutic agent AE37 in patients with prostate cancer. The study demonstrates an association between a specific immune response generated by AE37 and improved overall survival, as reported online in *Cancer Immunology, Immunotherapy* (July 23, 2014). While a prior study showed that AE37-immunized patients had better overall and disease-free survival as a group than would be expected from their disease status, the current study shows that patients with the strongest immunologic response fared best. In particular, both the presence of AE37-induced T cells in peripheral blood and a robust delayed-type hypersensitivity response elicited by AE37 correlated significantly with overall survival.

Application submitted for orphan status of bladder cancer agent

Bioniche has submitted to the FDA an application for organ drug designation for its Mycobaterial Cell Wall-Nucleic Acid (MCNA) Complex sterile suspension for the treatment of patients with bacillus Calmette-Guérin-refractory/relapsing high-grade nonmuscle-invasive bladder cancer. If approved, the designation of MCNA as an orphan drug will give the company a 7-year period of market exclusivity in the U.S. and a waiver to certain filing fees.

Multi-site trial expands development of bladder cancer diagnostic test

OncoCyte Corp. has expanded the clinical development of its urine-based bladder cancer diagnostic test by initiating a multi-site clinical trial. The trial, which will involve up to 1,200 patient samples obtained from at least four large urology clinics located throughout the United States, has received Institutional Review Board approval at multiple sites and was scheduled to begin enrolling patients in August 2014. OncoCyte's initial study of the PanC-Dx test began in January and involves pathology specimens being collected at a leading medical institution. The multi-site trial is designed to expand the potential use of the test beyond pathology laboratories and into urology practices at the point of cystoscopy. The goal of the current clinical trial is to compare the performance of OncoCyte's proprietary PanC-Dx bladder cancer markers to the performance of cystoscopy.

Research launched on ultrasound treatment for enlarged prostate

Research has begun on the development of a safe, noninvasive treatment for BPH. The experimental Vortx Rx device from HistoSonics, Inc. is based on histotripsy technology, a non-thermal focused ultrasound therapy that mechanically liquifies targeted tissues. Vortx Rx treatment involves using high-intensity sound waves like an acoustic scalpel to break down targeted cells into a liquid that leaves the body during urination. A U.S. pilot clinical study will enroll a limited number of men with BPH symptoms at trial sites including ProMedica and the University of Michigan in Ann Arbor. The primary goal of this pilot study is to demonstrate safety of the Vortx Rx in the treatment of BPH, ProMedica said.

Research agreement with Kaiser to examine bladder Ca test

Pacific Edge Ltd signed an agreement with Southern California Permanente Medical Group to research its user program to evaluate its Cxbladder bladder cancer technology within the clinical settings of Kaiser Permanente's health care network. The Kaiser user program research project is scheduled to recruit approximately 2,000 patients presenting with microscopic and macroscopic hematuria. Cxbladder is designed to provide clinicians with a means to identify patients with a high degree of surety who do not have bladder cancer so as to avoid further expensive clinical workup, according to Pacific Edge. The user program research is scheduled to begin later this year, with results completed in early 2015.

Speak Out

Have recent studies changed your approach to TRT?

"The risks of testosterone that I take more into account are the more classic ones, like worsening BPH, sleep apnea, and considering carefully whether to supplement somebody who has a history of prostate cancer. Those factors are contraindications to a person who has a lot of obstructive voiding symptoms and severe sleep apnea.

Dr. Anderson

I haven't had to deal with the idea of increased risk of heart attack, however. I don't have older men who are on testosterone; my practice doesn't really include the men covered in the studies. Talking about supplementing low testosterone to the normal range, I would look at the study to see why both would seem to be bad, because there are heart risks with low testosterone, too. I would look into it more carefully than I've had to right now."

Gregory Anderson, MD
Marshfield, WI

"There's data on either side of the seesaw to support either conclusion; there is data to suggest testosterone can be cardioprotective and data to suggest testosterone may trigger a symptomatic event.

If a patient's symptoms coincide with low-level testosterone and he doesn't have risk factors for testosterone supplementation, I offer him that. Then I follow good FDA guidance, and within the first 2 weeks, get a level. I start the patient at the lowest dosage. If his testosterone springs into the mid-range of 400-500 ng/dL, I leave him there and reassess twice a year.

Dr. Broderick

Screening in the urologist's office for cardiovascular disease is a matter of asking simple, straightforward questions about cardiovascular risk."

Gregory Broderick, MD
Jacksonville, FL

"I have a lot of conversations about the pros and cons of testosterone therapy. Various studies show that hypogonadal men have an increased risk of heart disease. But the studies were controversial, and other studies have indicated the opposite. I present both sides of the story. I tell men that, ultimately, it's like any other treatment; there's risk in anything we do or don't do.

About 90% of the people continue to use it, appropriately. I've had very few people back away once I've given them the pro and the cons.

This is the way I've always handled issues, but clearly discussion has increased in the past months. I've seen a lot of primary care doctors who were giving testosterone replacement get out of it. They say, 'Go see the urologist.' In some ways, we're seeing more patients because of these reports."

Kevin Perry, MD
Cary, NC

For patients with bone metastases from solid tumors

Prevent bone complications longer

In a prespecified integrated analysis of 3 pivotal trials (N = 5,723),
XGEVA® was proven to delay the median time to first bone complication by

8.2 months longer
vs zoledronic acid[1]

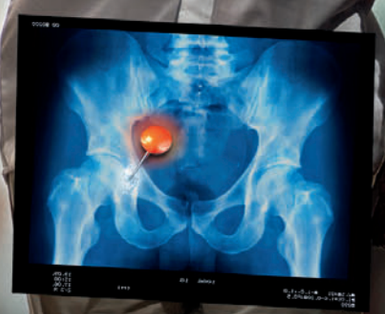
Data from a prespecified integrated analysis of three international, phase 3, double-blind, double-dummy, active-controlled trials comparing XGEVA® with zoledronic acid for the prevention of bone complications in patients with bone metastases from solid tumors or multiple myeloma. Denosumab was superior to zoledronic acid in reducing the risk of the first on-study bone complication by 17% (HR = 0.83 [95% CI: 0.76–0.90]; $P < 0.001$, superiority). The median time to first on-study bone complication was 27.7 months for denosumab versus 19.5 months for zoledronic acid, a difference of 8.2 months.[1]

Bone complications, or skeletal-related events (SREs), are defined as radiation to bone, pathologic fracture, surgery to bone, and spinal cord compression.[2,3]

Of those participating in the XGEVA® pivotal trials, 33% (n = 1,901) were patients with castration-resistant prostate cancer.[2]

Sub-Q INJECTION

XGEVA® is a convenient 120 mg subcutaneous injection administered once every 4 weeks.[2]



- RANK Ligand (RANKL) is produced by bone cells in the skeleton and is a key mediator of bone resorption[4]
- RANKL production is increased at sites of bone metastases, and stimulates osteoclasts to destroy bone[4]
- XGEVA® acts precisely to bind RANKL and inhibits osteoclast formation, function, and survival[2]
- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®[2]

XGEVA® is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

XGEVA® is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

Learn more at XGEVA.com/prostate

IMPORTANT SAFETY INFORMATION

Hypocalcemia

- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when XGEVA® is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.
- An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Hypersensitivity

- XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient

- Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) can occur in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure.
- Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®.
- Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

- Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
- Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Embryo-Fetal Toxicity

- XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.
- Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions

- The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.

Please see brief summary of Prescribing Information on the following page.

REFERENCES: 1. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. 2012;48:3082-3092. **2.** XGEVA® (denosumab) prescribing information, Amgen. **3.** Brodowicz T, O'Byrne K, Manegold C. Bone matters in lung cancer. *Ann Oncol*. 2012;23:2215-2222. **4.** Roodman GD. Mechanisms of bone metastasis. *N Engl J Med*. 2004;350:1655-1664.

BIOTECHNOLOGY BY AMGEN®

XGEVA®
(denosumab)

Subcutaneous injection.

www.XGEVA.com

Brief Summary: Consult package insert for complete Prescribing Information

XGEVA® (denosumab)

INDICATIONS AND USAGE:

Bone Metastasis from Solid Tumors. Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Important Limitation of Use. Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

DOSAGE AND ADMINISTRATION:

Recommended Dosage. The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

Preparation and Administration. Visually inspect Xgeva for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter. Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way. Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

CONTRAINDICATIONS:

Hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Xgeva.

Hypersensitivity. Xgeva is contraindicated in patients with known clinically significant hypersensitivity to Xgeva.

WARNINGS AND PRECAUTIONS: Drug Products with Same Active Ingredient. Xgeva includes the same active ingredient (denosumab) found in Prolia. Patients receiving Xgeva should not take Prolia.

Hypersensitivity. Clinically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Xgeva therapy permanently.

Hypocalcemia. Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. In the postmarketing setting, severe symptomatic hypocalcemia has been reported. Advise patients to contact a healthcare professional for symptoms of hypocalcemia. An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Osteonecrosis of the Jaw. Osteonecrosis of the jaw (ONJ) can occur in patients receiving Xgeva, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials, in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure. Seventy-nine percent of patients with ONJ had a history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor. Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Xgeva. Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture. Atypical femoral fracture has been reported with Xgeva. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During Xgeva treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Xgeva therapy should be considered, pending a risk/benefit assessment, on an individual basis.

EMBRYO-FETAL TOXICITY: Xgeva can cause fetal harm when administered to a pregnant woman. Based on findings in animals, Xgeva is expected to result in adverse reproductive effects. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth, and decreased neonatal growth. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after with the last dose of Xgeva. Apprise the patient of the potential hazard to a fetus if Xgeva is used during pregnancy or if the patient becomes pregnant while patients are exposed to Xgeva. Advise patients to contact their healthcare provider if they become pregnant or a pregnancy is suspected during this time.

ADVERSE REACTIONS: The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypocalcemia
- Osteonecrosis of the Jaw

The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea *(see Table 1)*. The most common serious adverse reaction in patients receiving Xgeva was dyspnea. The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

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 other clinical trials and may not reflect the rates observed in practice. The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required. The median duration of exposure to Xgeva was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received Xgeva, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

Table 1. Per-patient Incidence of Selected[a] Adverse Reactions of Any Severity (Trials 1, 2, and 3)

Body System	Xgeva n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/ Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving Xgeva in Trials 1, 2, and 3, and meeting one of the following criteria:

- At least 1% greater incidence in Xgeva-treated patients, or
- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo *(US Prescribing Information for zoledronic acid)*

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 – 8.5 mg/dL (2.075 – 2.125 mmol/L) for calcium and 2.2 – 2.8 mg/dL (0.71 – 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes.
- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15.4% of patients treated with Xgeva and 7.4% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw

In the primary treatment phases of Trials 1, 2, and 3, ONJ was confirmed in 1.8% of patients in the Xgeva group (median exposure of 12.0 months; range 0.1 – 40.5) and 1.3% of patients in the zoledronic acid group. The trials in patients with breast (Trial 1) or prostate (Trial 3) cancer included an Xgeva open label extension treatment phase where patients were offered Xgeva 120 mg once every 4 weeks (median overall exposure of 14.9 months; range 0.1 – 67.2). The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range: 4 – 53).

Atypical Subtrochanteric and Diaphyseal Fracture

Atypical femoral fracture has been reported with Xgeva.

Postmarketing Experience. Because postmarketing 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.

The following adverse reactions have been identified during post approval use of Xgeva:

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases.
- Hypersensitivity, including anaphylactic reactions.
- Musculoskeletal pain, including severe musculoskeletal pain. Positive rechallenge has been reported.

Immunogenicity. As with all therapeutic proteins, there is potential for immunogenicity. Using an

electrochemiluminescent bridging immunoassay, less than 1% (7/2758) of patients with osseous metastases treated with denosumab doses ranging from 30 – 180 mg every 4 weeks or every 12 weeks for up to 3 years tested positive for binding antibodies. No patient with positive binding antibodies tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based in vitro biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result 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 antibodies to denosumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS: No formal drug-drug interaction trials have been conducted with Xgeva. In clinical trials in patients with breast cancer metastatic to bone, Xgeva was administered in combination with standard anticancer treatment. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy. There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months were not altered by concomitant chemotherapy and/or hormone therapy. The median reduction in uNTx/Cr from baseline to month 3 was similar between patients receiving concomitant chemotherapy and/or hormone therapy.

USE IN SPECIFIC POPULATIONS:

Pregnancy: Category D. Risk Summary: Xgeva can cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. There are no adequate and well-controlled studies with Xgeva in pregnant women. Women should be advised not to become pregnant when taking Xgeva. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women who become pregnant during Xgeva treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Clinical Considerations: The effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. If the patient becomes pregnant during Xgeva therapy, consider the risks and benefits in continuing or discontinuing treatment with Xgeva.

Animal Data: The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a "knockout mouse"). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels). Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

Nursing Mothers. It is not known whether Xgeva is excreted into human milk. Measurable concentrations of denosumab were present in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Xgeva, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Maternal exposure to Xgeva during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. However, in cynomolgus monkeys treated with denosumab throughout pregnancy, maternal mammary gland development was normal, with no impaired lactation. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated.

Pediatric Use. Xgeva is not recommended in pediatric patients. The safety and effectiveness of Xgeva in pediatric patients have not been established. Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Xgeva therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth.

Geriatric Use. Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Renal Impairment. Two clinical trials were conducted in patients without cancer and with varying degrees of renal function. In one study, patients (N=55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a second study, patients (N=32) with severe renal dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, greater risk of developing hypocalcemia was observed with increasing renal impairment, and with inadequate/no calcium supplementation. Hypocalcemia was mild to moderate in severity in 96% of patients. Monitor calcium levels and, calcium and vitamin D intake.

Females and Males of Reproductive Potential. Contraception

Females: Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. Advise patients to contact their healthcare provider if they become pregnant, or a pregnancy is suspected, during treatment or within 5 months after the last dose of Xgeva. *Males:* The extent to which denosumab is present in seminal fluid is unknown. There is potential for fetal exposure to denosumab when a male treated with Xgeva has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

OVERDOSAGE: There is no experience with overdosage of Xgeva.

HOW SUPPLIED/STORAGE AND HANDLING: Xgeva is supplied in a single-use vial. Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label. Protect Xgeva from direct light and heat. Avoid vigorous shaking of Xgeva.

PATIENT COUNSELING INFORMATION:

Advise patients to contact a healthcare professional for any of the following:

- Symptoms of a hypersensitivity reaction, including rash, urticaria, pruritus, lip swelling, shortness of breath, hypotension and respiratory tract edema
- Symptoms of hypocalcemia, including paresthesias or muscle stiffness, twitching, spasms, or cramps
- Symptoms of ONJ, including pain, numbness, swelling of or drainage from the jaw, mouth, or teeth
- Persistent pain or slow healing of the mouth or jaw after dental surgery
- Symptoms of atypical femoral fracture, including new or unusual thigh, hip, or groin pain
- Pregnancy or nursing

Advise patients of the need for:

- Avoiding therapy with Xgeva if a serious allergic reaction occurred with prior Xgeva or Prolia therapy
- Proper oral hygiene and routine dental care
- Informing their dentist that they are receiving Xgeva
- Avoiding invasive dental procedures during treatment with Xgeva
- The use of highly effective contraception during and for at least 5 months after treatment with Xgeva for females of reproductive potential

Advise patients that denosumab is also marketed as Prolia®. Patients should inform their healthcare provider if they are taking Prolia.

Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Printed in USA.

AMGEN®
Oncology

Multiple stones: Watch for –59 modifier replacements

Medicare may be listening to argument over rule against charging for stones on same side

Coding Q&A

Ray Painter, MD, Mark Painter

Urologist **Ray Painter, MD**, is president of Physician Reimbursement Systems, Inc., in Denver and is also publisher of *Urology Coding and Reimbursement Sourcebook*. **Mark Painter** is CEO of PRS Urology SC in Denver.

Q Since we have the new code 52356, would you suggest that we bill for multiple stones in one kidney as follows:

- **52356**
- **52353**
- **52353-59-76?**

A For private, non-Medicare, payers, if you had three totally separate, non-contiguous stones that were treated with lithotripsy and then a stent was inserted, the above coding would be correct. However, for Medicare, the answer has changed. (Note that the answers to the second and third questions relate to this topic as well.)

We have been asked many times, "How could you talk about the same topic year after year after year?" Our answer is always simple: "You don't even have to change the questions, because the answers keep changing." Unfortunately, the answer to questions about modifier –59 and multiple stones has changed multiple times during the past few years. The current answer is that, for Medicare, you cannot charge separately for the treatment of multiple stones on the same side of the urinary tract.

"Same side" includes stones in the kidney, renal pelvis, or ureter regardless of mode of treatment. If the patient's insurance is Medicare, Medicaid, or another federally funded program that uses Medicare rules, you should report only one treatment per side.

The AUA received a letter several months ago from the director of the National Correct Coding Initiative (NCCI) indicating that it would be incorrect to use the –59 modifier to report separate treatments for any additional stone on the same side. We think he is absolutely incorrect in making this ruling. The AUA Coding and Reimbursement Committee agrees that it was incorrect and is appealing the decision.

Apparently, CMS also agrees that the ruling was incorrect, or at least the agency understands the problem. CMS issued a transmittal indicating four new modifiers will replace/supplement modifier –59 in January 2015. Stay tuned for suggestions on the correct uses of those modifiers in later publications. In short, the answer to this question will change again in January.

For Medicare patients, you cannot charge for more than one stone on the same side at the same setting regardless of how it is treated.

Q I have a question regarding CPT code 50590 (extracorporeal shock wave lithotripsy). All of my coding materials show that 50590 can only be billed one time per side, whether the urologist treated more than one stone in the kidney or kidney and ureter. Can you clarify this?

A As explained above, for Medicare patients, you cannot charge for more than one stone on the same side at the same setting, regardless of how it is treated.

ESWL presents a special problem in treating non-Medicare patients. The majority of ESWL cases are performed on single stones; therefore, reimbursement for the code is based on the work effort required to position and treat a single stone. So if a physician is treating a second stone, which requires a significant amount of additional time and effort, there should be a way to report an additional treatment with the appropriate modifier. How to report this remains up in the air.

CPT code 50590 includes no clear guidance on number of stones or number of treatments rendered. Some have interpreted the code to mean that ESWL is one charge, regardless of the number of stones or positions required. Others have interpreted the description to mean that each separately positioned ESWL should be coded separately.

An additional consideration should be given to the technical component. If an additional "shock plug" has to be used, then there should be a way to allow the facility to recoup the extra costs associated with the service.

Based on the interpretation that the code is all-encompassing for a single encounter, the best way to report the extra effort required for repositioning and treat-

Send coding and reimbursement questions to Ray Painter, MD, and Mark Painter c/o *Urology Times*, at UT@advanstar.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

Business of Urology THIS ISSUE

ment of separate stones would be to append modifier –22 to code 50590. Recall that this method of reporting will likely require supporting documentation and manual review.

Based on the interpretation that the code is in fact descriptive of a single positioning and treatment, reporting multiple ESWL positions for the treatment of multiple stones would allow for reporting 50590 for each new position/new stone during a treatment session. The current modifiers available to report more than one procedure are –51 (will not unbundle) and –59. Given current bundling and payment rules, –59 would likely be the appropriate modifier.

Either approach may require appeal and should be checked against any agreed-upon contract policy for the payer. Remember, Medicare has already offered an interpretation blocking reporting of multiple treatments on the same side.

Q We follow the NCCI guidelines that state the following relating to multiple stones:

"Some lesions of the genitourinary tract occur at mucocutaneous borders. The CPT Manual contains integumentary system (CPT codes 10000-19999) and genitourinary system (CPT codes 50000-59899) codes to describe various procedures such as biopsy, excision, or destruction. A single code from one of these two sections of the CPT Manual that best describes the biopsy, excision, destruction, or other procedure performed on one or multiple similar lesions at a mucocutaneous border should be reported. Separate codes from the integumentary system and genitourinary system sections of the CPT Manual may only be reported if separate procedures are performed on completely separate lesions on the skin and genitourinary tract. Modifier 59 should be utilized to indicate that the procedures are on separate lesions. The medical record should accurately describe the precise locations of the lesions."

Can you provide any clarification regarding this passage in NCCI and the correct coding for the treatment of multiple stones?

A The guidelines you have quoted specifically address lesions and are guidelines included in the NCCI manual. NCCI guidelines are developed under contract from Medicare to provide payment guidance to Medicare payers. It appears from your question that you have chosen to follow these guidelines for payers other than Medicare or payers specifically stating they will follow Medicare guidelines. We will answer your question as it applies to Medicare, but want to clarify that your application of the directive from Medicare to other payers is not required.

The guideline appears to focus on mucocutaneous lesions that may affect both the genitourinary tract and the integumentary system. Interpreting this strictly on the NCCI guideline quoted above, it would appear that NCCI is directing that treatment of a lesion that extends from the genitourinary tract out into the skin should be reported with a single code, either from the genitourinary section or the integumentary system of CPT.

Rather than the strict interpretation of the guideline listed, we are going to assume that the lesion reference is based on previous articles we have written regarding multiple stones. The reference to NCCI guidelines in our previous articles was specifically related to their inter-

Please see **MULTIPLE STONES,** page 32

Ureter injured during colostomy reversal

Lawsuit claims stent should have been placed prior to open sigmoid resection

Malpractice Consult

Dawn Collins, JD

Ms. Collins is an attorney specializing in medical malpractice in Long Beach, CA. She welcomes your feedback on this column at dawncfree@gmail.com.

A 63-year-old Pennsylvania woman went to the emergency room in 2010 due to nausea and vomiting. An abdominal/pelvic computed tomography scan revealed a constricting lesion in the sigmoid colon, possibly indicative of malignancy or diverticulitis.

A surgeon was consulted and the patient underwent an open sigmoid resection, decompression of the colon, and colostomy. She was discharged after about a week, and was seen within the next month by a nurse for ostomy-related in-home care.

The following month, the patient returned to the hospital with complaints of abdominal pain for 4 days after she had moved some heavy luggage. A CT scan revealed a large parastomal hernia, but no evidence of obstruction.

Eleven days later, she was seen by her surgeon, who noted a mild hernia next to the colostomy. The patient was given information regarding colostomy reversal and 6 days later she underwent this procedure, including a repair of the hernia.

Postoperatively, the patient was diagnosed with a ureter injury that required a cystoscopy and ureteroscopy with placement of a nephrostomy tube. A few months later, a ureterolysis and ureteral reimplantation were performed.

The woman sued the surgeon and claimed that actions should have been taken to protect the ureter due to her prior surgeries, including placement of a stent prior to surgery by a urologist.

The physician argued that injury to the ureter is a known complication of the procedure and that the patient was informed of this prior to the operation. A defense verdict was returned.

Chronic testicular pain following vasectomy

A 34-year-old New York man underwent a vasectomy in 2008, performed by his urologist. The patient developed chronic testicular pain, a spermatocele, and a hydrocele. He underwent removal of the hydrocele and a portion of the spermatocele in 2010, but continues to have pain.

The physician argued that injury to the ureter is a known complication of the procedure and the patient was informed of this prior to the operation.

The man sued his urologist and claimed lack of informed consent in that he was not told of the risk of chronic testicular pain syndrome.

The urologist argued that chronic testicular pain syndrome is not a significant risk of a vasectomy procedure and a defense verdict was returned.

LEGAL PERSPECTIVE: The standard of care for a risk/benefit discussion in obtaining informed consent does not require the disclosure of all possible risks and complications ever known to be associated with the particular procedure. Most states use a reasonable person standard; that is, a reasonable amount of information that a reasonable person would need to make a decision whether or not to have a procedure. In this case, the patient claimed that chronic testicular pain should have been discussed since "30% of vasectomies" result in this syndrome. As published recently in *Urology Times* ("How to manage testicular/groin pain: medical and surgical ladder," August 2014, page 16), it is estimated that some chronic pain is present in 1% to 15% of men following vasectomy. The urologist explained that the syndrome is not a significant risk and need not be specifically disclosed, and was successful in defending this case.

Claim that spinal tumor should have been found 2 years earlier

A Missouri man underwent a vasectomy in 2008, which was performed by his urologist. The patient had continuing urinary problems for years and eventually underwent prostate surgery 2 years later.

His problems with urinary and bowel incontinence worsened and he went to another urologist, who referred him to a neurosurgeon. A spinal tumor was found and the neurosurgeon performed an operation to remove it in 2012.

The man sued his first urologist and claimed he should have diagnosed the tumor 2 years earlier during treatment for his urinary symptoms.

The physician claimed the patient's urinary retention was normal 4 months after his prostate surgery, and the patient failed to return for a follow-up appointment after that exam. He argued that the patient did not seek a second opinion for another 15 months, over which time his symptoms had worsened and the spinal tumor was then diagnosed. A defense verdict was returned. UT

MULTIPLE STONES

continued from page 31

pretation of the use of modifier –59. Rather than rewrite those articles, we will summarize the position taken in them.

Our position was that stones are similar to lesions in that they can occur in the same organ system; they require separate work to treat if in fact multiple stones were diagnosed prior to the surgery and may require not only separate work effort but may also require separate techniques and clearly separate effort. If separately identified lesions are allowed to be paid separately, separate stones should be treated similarly and therefore could be called lesions.

This position created a bit of controversy, and as such, a request for clarification was sent to Medicare from the AUA. Medicare responded in a letter to the AUA specifically stating that stones are not lesions and therefore the guideline above cannot be applied to stones. Further, Medicare has stated that treatments of multiple stones are not allowed to be charged separately regardless of treatment method for the same side, as noted in the first question above. As also stated in the first question, the AUA has officially disagreed with this interpretation (not as it relates to the portion of the letter stating that stones are not lesions but to the fact that treating of multiple stones should not be separately reported) and it appears that Medicare may be listening; we will keep you posted.

In short, the NCCI guideline quoted above does not appear to apply to multiple stones. UT

In mCRPC therapy...

Is there more to the story?

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindications—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

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

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.

Increased ZYTIGA® Exposures With Food—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

mCRPC=metastatic castration-resistant prostate cancer; AST=aspartate aminotransferase; ALT=alanine aminotransferase.

Please see additional Important Safety Information on the next page.
Please see brief summary of full Prescribing Information on subsequent pages.

For men with mCRPC who progressed on ADT

In a clinical trial, patients had a median overall survival on ZYTIGA® (abiraterone acetate) of...*

More than 1,000 days. And every day tells a story.

35.3 MONTHS MEDIAN OVERALL SURVIVAL FOR ZYTIGA® plus prednisone† vs **30.1 MONTHS** with placebo plus prednisone (active compound).‡

5.2 MONTHS IMPROVEMENT IN MEDIAN OVERALL SURVIVAL compared with placebo plus prednisone.

Co-primary end point—overall survival: hazard ratio (HR)=0.792; 95% CI: 0.655, 0.956; *P*=0.0151; prespecified value for statistical significance not reached.

Co-primary end point—radiographic progression-free survival: median not reached for ZYTIGA® plus prednisone vs a median of 8.28 months for placebo plus prednisone. HR=0.425; 95% CI: 0.347, 0.522; *P*<0.0001.

IMPORTANT SAFETY INFORMATION (cont)

Increased ZYTIGA® Exposures With Food—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Hepatotoxicity—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

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

ADT=androgen-deprivation therapy.

Janssen Biotech, Inc.

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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

Drug Interactions—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. *In vitro*, ZYTIGA® inhibits CYP2C8. There are no clinical data on the use of ZYTIGA® with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

Use in Specific Populations—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

†At a prespecified interim analysis for OS, 37% (200/546) of patients treated with ZYTIGA® plus prednisone compared with 43% (234/542) of patients treated with placebo plus prednisone had died.

‡Prednisone, as a single agent, is not approved for the treatment of prostate cancer.

003307-130924

Learn more today at
www.zytigahcp.com.

Every day tells a story.

once-daily
Zytiga®
(abiraterone acetate)
250 mg tablets

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.
- Increased ZYTIGA Exposures with Food *[see Warnings and Precautions]*.

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

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

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

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

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

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

Table 1: Adverse Reactions due to ZYTIGA in Study 1

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

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

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

Table 2: Laboratory Abnormalities of Interest in Study 1

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

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

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

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

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

ZYTIGA® (abiraterone acetate) Tablets

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

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

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

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

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

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

[1]Based on non-fasting blood draws

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

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

Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. 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.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information].*

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

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

ZYTIGA® (abiraterone acetate) Tablets

OVERDOSAGE

Human experience of overdose with ZYTIGA is limited.

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

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

Manufactured by:
Patheon Inc.
Mississauga, Canada

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

Revised: May 2014

015924-140528

janssen

Could your EHR system put patients at risk?

Potential pitfalls include computerized order entry-related errors, data display mismatches

One of the most dominant conversations in urology practices today concerns the impact of adopting health information technology on providers, processes, and even profitability. Sometimes lost in the conversation is the impact of electronic health record adoption on the patient—the recipient of those care processes and care providers. In this article, I will discuss what you need to know about EHRs and patient safety.

CPOE frequently studied

A number of studies appear to demonstrate a relationship between adoption of EHRs and patient safety. One of the most thoroughly studied areas is that of the impact of computerized provider order entry (CPOE) on medication errors. In a controlled trial, Bates et al demonstrated a significant decrease in potential (84%) and actual preventable (17%) adverse drug events when CPOE was employed (*JAMA* 1998; 280:1311-6). In the pediatric literature, studies show conflicting findings of increased mortality (*Pediatrics* 2005; 116:1506-12) and decreased mortality (*Pediatrics* 2010; 126:14-21) coincident with adoption of CPOE.

CPOE adoption can introduce unintended consequences—an effect that has been studied by Ash et al (*J Am Med Inform Assoc* 2007; 14:415-23) and others. One of the most important of these is the introduction of new kinds of errors; for example, the juxtaposition of medications in a list that can lead to selection of incorrect drugs or incorrect dosages. Finally, the phenomenon of "alert fatigue"—which can lead a user to override important safety warnings in the context of "too many alerts"—should be a cautionary tale familiar to most medication prescribers. It is fair to say that CPOE comes with benefits and risks, and the user of these systems should be familiar with avoidable pitfalls that can lead to safety concerns.

EHRs present other safety concerns that have been recently analyzed in one of the most mature health care organizations—the Veterans Health Administration—by Meeks et al (*J Am Med Inform Assoc*, June 20, 2014 [online]). They report on 100 closed safety investigations related to EHRs over almost 4 years. As explained in the Meeks article, concerns can be classified by magnitude: adverse events that actually occurred, near misses, or unsafe conditions with the potential to harm a patient. Concerns may be classified by cause: unsafe design of the software or user interface, poor user training or user behaviors, organizational culture, or rules and regulations. All of these causes can be seen in various combinations.

In their research, Meeks et al found that the most common category of safety concern was a mismatch between the information needs of the user and the EHR content display. Examples cited include requiring a user to navigate multiple screens to determine the status of a patient or a medication list, functionality allowing order entry on two patients at the same time, inconsistent user interface wording and function across the application, and order entry dialog allowing conflicting information to be entered. Other major categories of concern were those caused by software upgrades, those caused by interfaces of the EHR to other systems or components, and hidden dependencies in the system.

Practice Pointers

- A number of studies appear to demonstrate a relationship between adoption of EHRs and patient safety.
- The adoption of computerized provider order entry can introduce new errors, such as the juxtaposition of medications in a list that can lead to selection of incorrect drugs or incorrect dosages.
- Meeks et al found that the most common category of EHR safety concern was a mismatch between the information needs of the user and the EHR content display.
- Strategies to mitigate EHR safety issues include robust testing, documentation of organizational work flows, and establishing monitoring and measuring practices.

The Bottom Line

Robert A. Dowling, MD

Dr. Dowling is an independent consultant, the former medical director of a large metropolitan urology practice, and the consulting medical director for Healthtronics IT Solutions. He resides in Fort Worth, TX.

In their paper, Meeks et al offered strategies to mitigate these safety concerns, including robust testing, documentation of organizational work flows, and establishing monitoring and measuring practices. Walker et al have enumerated steps that organizations and EHR vendors can take to prevent safety-related incidents (*J Am Med Inform Assoc* 2008; 15:272-7, [table 2]).

EHR-related safety events common

How prevalent are these EHR safety concerns outside of the VA system? In a recent survey of health care attorneys and risk managers (369 respondents), more than half reported a serious EHR-related safety event in the last 5 years (*J Healthc Risk Manag* 2014; 34:14-26). The most common types of concerns were related to data display and CPOE, similar to the VA experience cited above. The top three variables mentioned by respondents were work flow process, user training and experience, and degree of EHR integration with existing organization systems.

Bottom line: Urologists should be aware that the benefits of EHR adoption are accompanied by potential risks. Safety concerns identified in numerous articles include incomplete displays leading to misinterpretation, user interfaces that contribute to data entry error, ignoring built-in decision support because of alert fatigue, and others. Urologists and their organizations should be alert to these concerns and incorporate tools such as work flow analysis, ongoing training, reporting of safety incidents, and dialogue with their vendor to reduce and prevent harm to patients. UT

UT Table

EHR safety: Organizational and vendor strategies

Use EHRs as tools for care-process redesign
Design and implement safe EHRs
Improve EHR safety testing and reporting
Prevent and manage EHR-related incidents
Communicate safety flaws and incidents
Develop and communicate EHR safety best practices

Source: Adapted from *J Am Med Inform Assoc* 2008; 15:272-7

Long-term care coverage: Know your options

Type of benefits, dollar limitations among determinants of premium pricing

Money Matters

Joel M. Blau, CFP, Ronald J. Paprocki, JD, CFP, CHBC

Joel M. Blau, CFP, (top) is president and **Ronald J. Paprocki, JD, CFP, CHBC,** is chief executive officer of MEDIQUS Asset Advisors, Inc. in Chicago. They can be reached at 800-883-8555 or blau@mediqus.com or paprocki@mediqus.com.

Q My elderly parents are starting to look at alternative senior living facilities. What are the major differences and options for long-term care insurance?

A The aging of America has forced many senior citizens and their families to explore the myriad housing options available today. When faced with the difficult prospect of changing one's normal style of living, the major factors to consider are age, interests, finances, and of course, health issues and concerns. Available elderly housing choices include independent living, assisted living, nursing homes, continuing care communities, and remaining at home.

Independent living housing is an attractive option for active seniors who can take care of themselves and prefer a social versus medical setting. Independent living facilities typically can accommodate a broad range of lifestyles. Often included are in-house activities and transportation to shopping and other outside events. Many also have dining rooms that serve daily meals, though most independent living facilities include a full kitchen within the resident's apartment or living unit. Residents can enjoy daily activities without worrying about the typical maintenance and repairs of individual home ownership.

Assisted living facilities essentially are communities designed for seniors who have some level of difficulty living and managing on their own. They provide a moderate level of personal care, including assistance with bathing and administering medications. Individual living units, which are usually rented on a monthly basis, are often of the efficiency style, with very limited kitchens or no cooking facilities at all. Additional care may be available to residents at an additional cost. The assisted living option is a good choice for the elderly who can manage with some limited help from on-staff aides.

Nursing homes offer a much more intense level of medical care and attention, usually under the supervision of a medical doctor. With so many other elderly care options available today, nursing homes have become geared toward dementia patients, limited rehabilitation stays, or patients near the end of their lives. Nursing homes can provide near-hospital-quality medical care for chronic illnesses.

Continuing care communities, also known as life care communities, attempt to provide facilities for all stages of aging within the same housing complex, and include independent and assisted living, as well as nursing and rehabilitative care. Costs include substantial entry fees plus monthly payments. The major advantage to this arrangement is the ease of movement between levels of care as the resident's condition changes. From a social standpoint, seniors may still maintain contact with friends as they move within the community.

Staying at home, with its familiar surroundings and proximity to friends and neighbors, remains the top choice for many seniors. By avoiding change, seniors can maintain an important sense of independence. Hired care can be tailored to specific situations, and the aides provide a more personal, one-on-one care environment. The difficulty comes with transportation issues relative to shopping and other errands, as well as the relatively high level of turnover of home health aides.

From a financial planning standpoint, it is critical to address long-term care issues in coordination with other risk management issues. To insure this risk, a number of insurers provide a variety of long-term care insurance products.

As with disability coverage, the benefits covered in a long-term care insurance policy as well as the dollar limitations dictate the pricing of the policy. Begin by determining what levels of care you would like to insure against. Definitions within the policies may include the following:

- **Skilled care:** Physician-ordered daily nursing and possibly rehabilitation care under the supervision of licensed skilled registered nurses and other skilled medical personnel
- **Intermediate care:** Same skilled personnel as above, except care is required only occasionally, not daily
- **Custodial care:** Based on doctor's orders, assistance may be covered within the policy for help with daily activities such as bathing, eating, dressing, mobility issues, etc. The assistance generally does not need to be provided by skilled medical personnel.

Other determinants of premium pricing include maximum allowable daily dollar limitations, inflation protection, guaranteed renewability, and a waiver of premium based on a specified number of days spent in a nursing home.

Q What is the AMT?

A The alternative minimum tax (AMT) system is designed to ensure that taxpayers pay a minimum amount of tax when they use certain tax benefits to reduce their regular tax liability. For planning purposes, the most common triggers of the AMT are large capital gains, higher-than-average number of dependency options, and large deductions for state income taxes. If your AMT is higher than your regular taxes, you pay the additional amount. The AMT rates are 26% for AMT income less than $182,500 and 28% for amounts over $182,500. UT

Financial Tips

- When faced with the difficult prospect of changing one's normal style of living, the major factors to consider are age, interests, finances, and health issues.
- Determinants of long-term care insurance premium pricing include maximum allowable daily dollar limitations, inflation protection, guaranteed renewability, and a waiver of premium based on a specified number of days spent in a nursing home.
- Definitions within long-term care insurance policies might include skilled care, intermediate care, or custodial care.
- The alternative minimum tax system is designed to ensure that taxpayers pay a minimum amount of tax when they use certain tax benefits to reduce their regular tax liability.

Send us your questions

Send your questions about estate planning, retirement, and investing to Joel M. Blau, CFP, c/o *Urology Times*, at UT@advanstar.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative. The publisher is not engaged in rendering legal advice.

CLINICS

continued from page 1

in *Time* magazine's recent cover article, "Manopause?! Aging, insecurity and the $2 billion testosterone industry" (July 31, 2014). Multidisciplinary collaboration is key for the success and credibility of a men's health center, according to Hunter Wessells, MD, professor and chair of urology at the University of Washington School of Medicine and staff member of the UW Medicine Men's Health Center, Seattle.

"Not all men's health centers are the same. Some are testosterone mills that are run by people with very little training in urologic diseases and are likely to be non-specialists. And some of them are very committed to improving the health of men," Dr. Wessells said.

Dr. Hotaling says he sees at least one patient

"What we're starting to appreciate is that there are a lot of problems that really are above the waistline that are contributing to conditions below the waistline."

STEVEN LAMM, MD

a week who is infertile because he has been inappropriately placed on testosterone at one of the "shot clinics."

"A lot of these testosterone clinics don't even see these patients. It's all done over the Web. And they charge them about $400 a month for their testosterone and for monitoring their therapy. What's difficult about testosterone is everyone will feel better if you put them on it. So it really requires some expertise to be able to ascertain who should be on it and shouldn't be on it," Dr. Hotaling said.

The University of Utah's men's health clinic center features flat-screen TVs in both the waiting room and procedure rooms. (Photo courtesy of University of Utah Health Care)

UW Medicine looked at the formation of its men's health center as a healthy alternative to testosterone and erectile dysfunction mills, according to Thomas J. Walsh, MD, associate professor of urology and director of the UW Medicine Men's Health Center.

"Our model of delivering care is not a financial or mercantilistic model; it's more of a complete care model," Dr. Walsh said.

Models vary

Richard S. Pelman, MD, clinical professor of urology at the University of Washington and a course director of the AUA's postgraduate course on male health, said he has introduced the course by asking attendees what men's health represents to them.

"To some, men's health represents reproductive health; to others, it may represent sexual health; to others, it may represent prostate health. It may be packaged into a longevity clinic and, recently, it may represent a testosterone replacement therapy clinic," Dr. Pelman said.

The concept of the faculty involved in the AUA course and the original AUA Ad Hoc Committee on Male Health was much more encompassing, according to Dr. Pelman.

An exam room at the Iris Cantor Men's Health Center at NewYork-Presbyterian/ Weill Cornell offers a sleek, high-tech look. (Photo courtesy of Walter Dufresne/ NewYork-Presbyterian Hospital)

"The concept of male health was to help urologists expand from the traditional model of directed evaluation and therapy of the GU organ to an expanded concept of systemic disease as it impacts that organ and how the GU issue may impact systemic disease," he said. "The urologist role would expand to a 'recognition and refer' role as issues were identified.

"What we're moving toward is a model where these guys come in and essentially get all or most of their health care needs met in one visit."

JAMES M. HOTALING, MD, MS

The obvious example is cardiometabolic disease and sexual health.

"Urologists should no longer limit their involvement to evaluation of ED and treatment. They must alert the patient as to the association of cardiometabolic disease and ED, and if the patient has not visited a medical provider recently, they need to at a minimum make that man an appointment with a primary care practice."

While even this men's health center model varies from center to center, there is a consistent focus on male-specific multidisciplinary care, with the goal of streamlining men's health care experiences.

Some centers act more as portals to care, focusing on low testosterone and erectile dysfunction, but screening men for other health issues and having in place a referral network. Others are more comprehensive.

Commonly, men's health centers are run

Please see **CLINICS,** on page 42

CLINICS

continued from page 41

by internists or urologists—sometimes both. Often, other specialists keep hours at the center.

New to the scene

All are fairly recent pioneers into this model of care. The first multidisciplinary men's health center to open in the U.S. was the Men's Health Center at The Miriam Hospital, Providence, RI, which opened in 2008. The model of care there is in-depth management of male sexual dysfunction, exploration of relationships to any potential incident coronary artery disease with a medical workup, a cardiometabolic evaluation, and stratification of patients at risk for cardiovascular events, including heart attack and stroke, according to Martin Miner, MD, co-director, Men's Health Center at The Miriam Hospital and clinical associate professor of family medicine and urology at Brown University's Warren Alpert Medical School.

Dr. Miner, an internist with urologic training, co-directs the clinic with urologist Mark Sigman, MD. The center is a portal for men who might need additional care by a cardiologist or other physician, Dr. Miner said.

"We have two full-time internal medicine specialists, a PA, three part-time urologists,

"Urologists should no longer limit their involvement to evaluation of ED and treatment."

RICHARD PELMAN, MD

and two psychologists (one part-time, one full-time). We have a physical therapist," Dr. Miner said.

The men's health center at the University of Utah has two urologists who work one day a week at the clinic, along with two (soon to be three) physician assistants.

"We're hiring a sexual therapist. Then we have cardiologists and primary care and some sleep medicine doctors, who we work with and refer to. We also have a nutritionist and a few other people who we work a lot with to optimize the care for these men," Dr. Hotaling said.

While some of those doctors are not on-site, they are part of the University of Utah's outpatient clinic, which houses the men's center, he says.

"If someone really needs to see a primary care doctor, I can literally walk them down the hall and get them in that day," Dr. Hotaling said.

Dr. Hotaling says the men's health center is moving toward a process where patients are screened on the phone for which doctors to see first, then booked for those appointments in one visit, he says.

Opened for more than a year, the UW Medicine men's health center is a similar model, directed by a urologist, but including urologists and general practitioners, according to Dr. Wessells.

"Our model does not cover the whole spectrum of cardiovascular disease, sleep disorders, and sees itself as a portal entry into health care for men. We focus on male reproductive, sexual, and urinary problems and work to link men both with other specialists and with primary care providers," Dr. Wessells said.

NewYork-Presbyterian/Weill Cornell Medical Center in New York opened its Iris Cantor Men's Health Center in July 2012, according

to Steven A. Kaplan, MD, the center's director.

"Traditionally, men's health models were run, at least in the academic world, by internal medicine people," said Dr. Kaplan, who is professor of urology at Weill Cornell Medical College. "I think it was the first time at Cornell that we were able to coalesce different departments—urology and medicine—under one banner. It demonstrated that you could actually bring in multiple different stakeholders under one roof. One entry system; one exit system."

Dr. Kaplan says his vision for a men's health center is a one-stop center for dealing with the most common things that men who access the health care system want. He says this includes urologic health, sexual health, urinary issues, cancer screenings, cardiac health, issues related to obesity and diabetes, sports medicine, psychological health, diet, and exercise.

"We don't do all of that. But if I had my wish list, it would include these areas to handle it all in one center," Dr. Kaplan said.

NYU's men's health center has 24 clinicians on staff, with expertise in internal medicine, pulmonary medicine, orthopedics, psychology, gastroenterology, rheumatology, otolaryngology, dermatology, psychiatry, and more. Four of the doctors there are urologists.

Some of the more established women's centers can make good models for men's centers. NYU created its male health center, which opened in January 2014, based on NYU's Tisch Center for Women's Health, developed years earlier, according to Dr. Lamm.

Attaching the men's health concept to a practice or clinic is more than a name or an advertising and marketing tool, according to Dr. Kaplan. The concept of holistic care means that a urologist who sees an obese patient with sexual dysfunction will address diabetes, lipidemia, and hypertension, and might walk the patient down the hall to visit with the center's internist or cardiologist, if needed.

The reception area at the University of Washington's UW Men's Health Center offers an inviting entrance. (Photo courtesy of Clare McLean/UW Medicine)

"We focus on male reproductive, sexual and urinary problems and work to link men, both with other specialists and with primary care providers."

HUNTER WESSELLS, MD

"It's a philosophy that we think beyond our own specialties," Dr. Kaplan said.

Key components

Men want one-stop-shopping, those who direct centers say.

"If you ask a man to go across the street to give blood and urine, he'd rather pee in his pants than have to go across the street," Dr. Lamm said. "You have to make it easy for these guys. I've said if a man comes to you with a spear in his head, you don't take the spear out right away until you've measured his blood sugar and blood pressure because if you take the spear out, he's going to leave."

A male-centered clinic should know how to work with men.

"You have to understand how to deal with men," Dr. Lamm said. "We do not criticize men for their obesity, drinking, or smoking. We're here to assist them and provide a safe place and a place where we can advise them about how to get healthier, more competitive, and how to proceed in life."

Expertise is important. For example, UW Medicine assembled a group of experts not only in their respective specialties but also in men's health, according to Dr. Walsh.

Man cave-like

These experts say men's health centers should have separate waiting rooms that look inviting to men.

The University of Utah center is decorated in darker colors and offers flat-screen televisions not only in the waiting room, but also in the procedure rooms. A selection of magazines that men like to read is a must, according to Dr. Hotaling.

"We tend to have a sports channel on in [the waiting room]," Dr. Wessells said. "During the World Cup, there were a lot of people watching the game in there."

UW Medicine is among the clinics that's isolated, according to Dr. Walsh.

"We are not housed within the general urology clinic that sees women with incontinence or men with prostate cancer. Rather, we are a clinic that is very specific to men's health conditions, like ED, hypogonadism, reproductive failure, BPH, and issues that arise after cancer treatment," Dr. Walsh said. "We needed a unique physical space that was defined by walls as a men's health center.

"And that's exactly what we did. We created an environment that was inviting and masculine. It was staffed with people who were accustomed to the unique needs of men and had all the accoutrements that make men comfortable."

Selling the concept

Selling the concept to the institution is critical, center directors say.

One important selling point is that a men's health center drives other referrals and business for hospitals, academic centers, and multispecialty group practices.

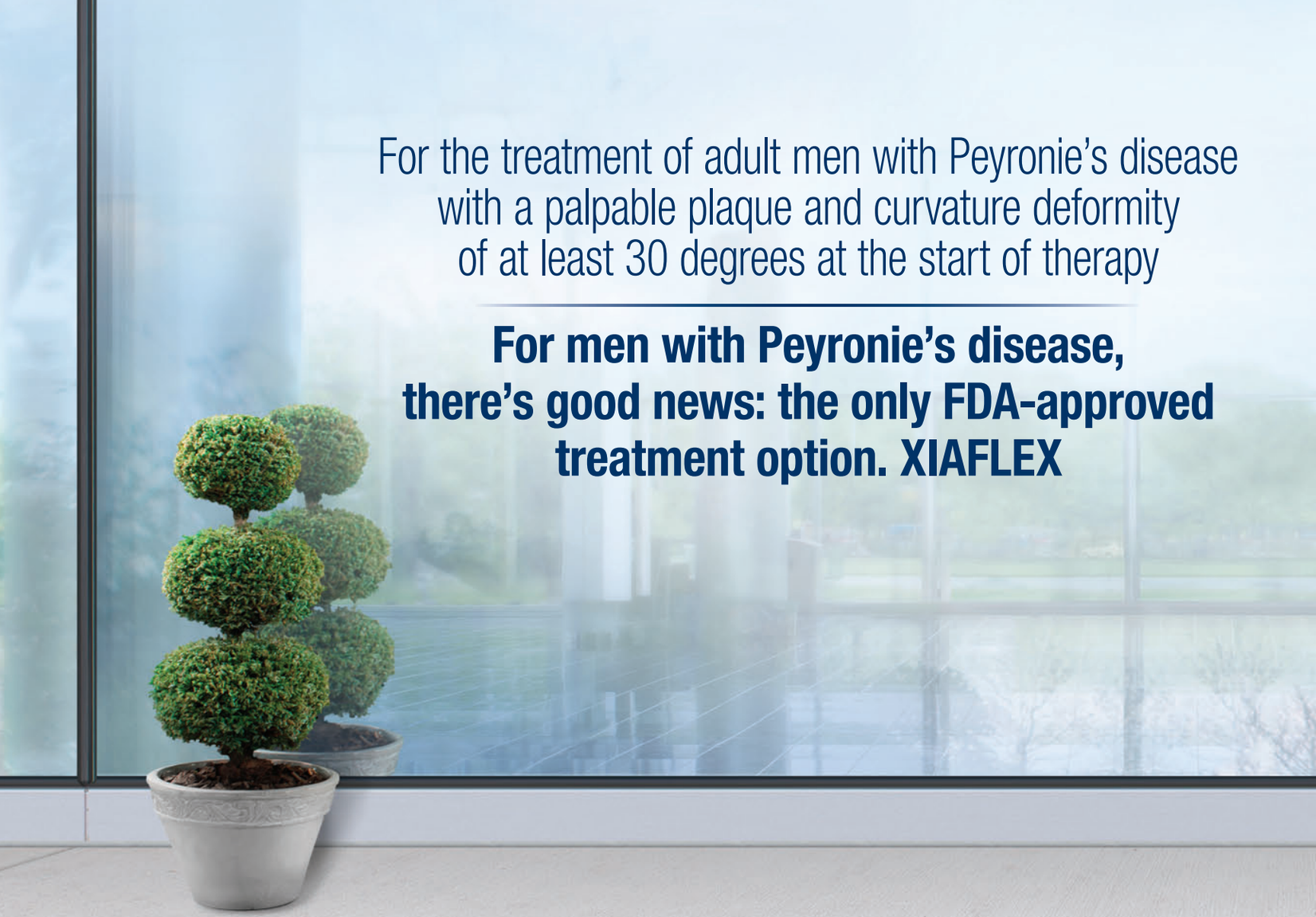
Although UW is a nonprofit organization,

Please see **CLNICS,** on page 47

MEETING A NEED: STATISTICS TELL THE STORY

Men are more likely than women to smoke and drink, make unhealthy or risky choices, and put off regular checkups and medical care, according to the National Institutes of Health. In addition, statistics from the Agency for Healthcare Research and Quality show that men are:

- **24%** less likely than women to have visited a doctor in the last year.
- **22%** more likely to have neglected their cholesterol tests.
- **32%** more likely to be hospitalized for long-term diabetes complications and 28% more likely than women to be hospitalized for congestive heart failure.



For the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

For men with Peyronie's disease, there's good news: the only FDA-approved treatment option. XIAFLEX

Important Safety Information

WARNING: CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PEYRONIE'S DISEASE

Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX-treated patients in clinical studies. In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX-treated patients.

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX is available for the treatment of Peyronie's disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX REMS Program.

- XIAFLEX is contraindicated in the treatment of Peyronie's plaques that involve the penile urethra due to potential risk to this structure and in patients with a history of severe allergic reaction to XIAFLEX or to collagenase used in any other therapeutic application or application method
- Injection of XIAFLEX into collagen-containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX should be injected only into the Peyronie's plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis

AUXILIUM
Innovations for Life®

- In the double-blind, placebo-controlled portions of the clinical trials in Peyronie's disease, a greater proportion of XIAFLEX-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX injection procedures). The incidence of XIAFLEX-associated pruritus was similar after each injection regardless of the number of injections administered
- Because XIAFLEX contains foreign proteins, severe allergic reactions to XIAFLEX can occur. Although there were no severe allergic reactions observed in the XIAFLEX clinical studies (eg, those associated with respiratory compromise, hypotension, or end-organ dysfunction), an anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to XIAFLEX for the treatment of Dupuytren's contracture, demonstrating that severe reactions including anaphylaxis can occur following XIAFLEX injections. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX injections. The safety of more than one treatment course of XIAFLEX is not known
- In the XIAFLEX controlled trials in Peyronie's disease, 65.5% of XIAFLEX-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis. Patients with abnormal coagulation (except for patients taking low-dose aspirin, eg, up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low-dose aspirin, eg, up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. In addition, it is recommended to avoid use of XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin)
- In the XIAFLEX clinical trials for Peyronie's disease, the most frequently reported adverse drug reactions (≥25%) and at an incidence greater than placebo included: penile hematoma, penile swelling, and penile pain

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

For more information, call 1-877-XIAFLEX, or visit XIAFLEX.com/hcp.

XIAFLEX®
collagenase clostridium histolyticum

XIAFLEX® (collagenase clostridium histolyticum) for injection, for intralesional use

Brief Summary of Prescribing Information

For complete information, see the full prescribing information for XIAFLEX.

WARNING: CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PEYRONIE'S DISEASE

Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX-treated patients in clinical studies. In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX-treated patients *[see Warnings and Precautions]*.

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention *[see Warnings and Precautions]*.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX is available for the treatment of Peyronie's disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX REMS Program *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

XIAFLEX is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

CONTRAINDICATIONS

XIAFLEX is contraindicated in:

- the treatment of Peyronie's plaques that involve the penile urethra due to potential risk to this structure.
- patients with a history of severe allergic reaction to XIAFLEX or to collagenase used in any other therapeutic application or application method *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Corporal Rupture (Penile Fracture) or Other Serious Injury to the Penis in the Treatment of Peyronie's Disease

Corporal rupture was reported as an adverse reaction after XIAFLEX injections in 5 of 1044 (0.5%) XIAFLEX treated patients in the controlled and uncontrolled clinical trials in Peyronie's disease.

In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture can not be excluded. These patients were managed without surgical intervention, but the long-term consequences are unknown.

Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie's disease *[see Adverse Reactions]*.

Signs or symptoms that may reflect serious injury to the penis should be promptly evaluated in order to assess for corporal rupture or severe penile hematoma, which may require surgical intervention.

Injection of XIAFLEX into collagen-containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX should be injected only into the Peyronie's plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis.

XIAFLEX REMS Program

Because of the risks of corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie's disease, XIAFLEX is available only through the **XIAFLEX REMS Program** *[see Warnings and Precautions]*.

Required components of the **XIAFLEX REMS Program** include the following:

- Prescribers must be certified with the program by enrolling and completing training in the administration of XIAFLEX treatment for Peyronie's disease.
- Healthcare sites must be certified with the program and ensure that XIAFLEX is only dispensed for use by certified prescribers.

Further information is available at www.XIAFLEXREMS.com or 1-877-313-1235.

Allergic Reactions

In the double-blind, placebo-controlled portions of the clinical trials in Peyronie's disease (Studies 1 and 2), a greater proportion of XIAFLEX-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX injection procedures). The incidence of XIAFLEX-associated pruritus was similar after each injection regardless of the number of injections administered.

Because XIAFLEX contains foreign proteins, severe allergic reactions to XIAFLEX can occur. Although there were no severe allergic reactions observed in the XIAFLEX clinical studies (e.g., allergic reactions associated with respiratory compromise, hypotension, or end-organ dysfunction), an anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to XIAFLEX for the treatment of Dupuytren's contracture, demonstrating that severe reactions including anaphylaxis can occur following XIAFLEX injections. Some patients with Dupuytren's contracture developed IgE-anti-drug antibodies in greater proportions and higher titers with successive XIAFLEX injections. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX injections. The safety of more than one treatment course of XIAFLEX is not known.

Risk of Bleeding in Patients with Abnormal Coagulation

In the XIAFLEX controlled trials in Peyronie's disease (Studies 1 and 2), 65.5% of XIAFLEX-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis (see Adverse Reactions Table). Patients with abnormal coagulation (except for patients taking low-dose aspirin, e.g., up to 150 mg per day) were excluded from participating in these studies.

Therefore, the efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low-dose aspirin, e.g., up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. In addition, it is recommended to avoid use of XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

ADVERSE REACTIONS

The following serious adverse reactions in patients with Peyronie's disease are discussed in greater detail elsewhere in the labeling:

- Corporal rupture (penile fracture) and severe penile hematoma *[see Warnings and Precautions]*
- In other XIAFLEX-treated patients, a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded *[see Warnings and Precautions]*

Clinical Studies Experience in Patients with Peyronie's Disease

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

In the controlled and uncontrolled clinical studies of XIAFLEX in Peyronie's disease, 1044 patients received a total of 7466 XIAFLEX injections.

Corporal Rupture and Other Serious Penile Injury

- Corporal rupture was reported as an adverse reaction after XIAFLEX injections in 5 of 1044 (0.5%) XIAFLEX treated patients.
- In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences are unknown.
- Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie's disease *[see Adverse Reactions]*.

The data described below are based on two identical, pooled, randomized, double-blind, placebo-controlled, multi-center trials through Day 365 in patients with Peyronie's disease (Studies 1 and 2). These trials included 832 patients of whom 551 and 281 received XIAFLEX and placebo, respectively. In these trials, patients were given up to 4 treatment cycles of XIAFLEX or placebo. In each cycle, two injections of XIAFLEX or two injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed at the study site on patients 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately 6-week intervals up to three additional times, for a maximum of 8 total injection procedures and 4 total modeling procedures *[see Clinical Studies in the full Prescribing Information]*.

The majority of Peyronie's patients experienced at least one adverse reaction (92% XIAFLEX-treated patients, 61% placebo-treated). Most adverse reactions were local events of the penis and groin and the majority of these events were of mild or moderate severity, and most (79%) resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered.

The most frequently reported adverse drug reactions (≥ 25%) in the XIAFLEX clinical trials in patients with Peyronie's disease were penile hematoma, penile swelling, and penile pain. The Adverse Reactions Table below shows the incidence of adverse reactions that were reported in greater than or equal to 1% of XIAFLEX-treated patients and at a frequency greater than placebo-treated patients after up to 8 injections in the pooled placebo-controlled trials through Day 365.

Adverse Reactions Occurring in ≥ 1% of XIAFLEX-Treated Patients with Peyronie's disease and at a Greater Incidence than Placebo After Up to Four Treatment Cycles in Studies 1 and 2 Combined

Adverse Reaction	XIAFLEX N=551	Placebo N=281
All Adverse Reactions	84.2%	36.3%
Penile hematoma[a]	65.5%	19.2%
Penile swelling[b]	55.0%	3.2%
Penile pain[c]	45.4%	9.3%
Penile ecchymoses[d]	14.5%	6.8%
Blood blister	4.5%	0
Penile blister	3.3%	0
Pruritus genital	3.1%	0
Painful erection	2.9%	0
Erectile dysfunction	1.8%	0.4%
Skin discoloration	1.8%	0
Procedural pain	1.6%	0.7%
Injection site vesicles	1.3%	0
Localized edema	1.3%	0
Dyspareunia	1.1%	0
Injection site pruritus	1.1%	0
Nodule	1.1%	0
Suprapubic pain	1.1%	0

[a] Includes: injection site hematoma and penile hematoma were reported with the verbatim term of penile bruising or injection site bruising in 87% of subjects.

[b] Includes: injection site swelling, penile edema, penile swelling, local swelling, scrotal swelling, and injection site edema.

[c] Includes: injection site pain, penile pain, and injection site discomfort.

[d] Includes: contusion, ecchymoses, penile hemorrhage, and injection site hemorrhage.

Severe penile hematoma or severe injection site hematoma were reported in 33/551 (6.0%) of XIAFLEX-treated patients and 0/281 (0%) of placebo-treated patients, in Studies 1 and 2 combined.

Reports of penile "popping" sounds or sensations

A popping noise or popping sensation in the penis, sometimes described as "snapping" or "cracking", and sometimes accompanied by detumescence, hematoma and/or pain, were reported in 73/551 (13.2%) XIAFLEX-treated patients and 1/281 (0.3%) placebo-treated patients.

There were no clinically meaningful differences in the incidence of adverse events following treatment with XIAFLEX based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

XIAFLEX was not associated with shortening of penile length in clinical trials in the treatment of Peyronie's disease.

Immunogenicity

During clinical studies in Dupuytren's contracture and Peyronie's disease, patients were tested at multiple time points for antibodies to the protein components of XIAFLEX (AUX-I and AUX-II).

In the Peyronie's disease clinical studies, at 6 weeks after the first treatment cycle of XIAFLEX 0.58 mg, approximately 75% of patients had antibodies against AUX-I and approximately 55% of patients had antibodies against AUX-II. Six weeks after the eighth injection (fourth treatment cycle) of XIAFLEX, >99% of XIAFLEX-treated patients developed high titers of antibodies to both AUX-I and AUX-II. Neutralizing antibodies were assayed for a subset of 70 samples selected to be representative of high and low titer binding antibody responses at week 12 of treatment. For each subject in whom a Week 12 sample was selected, the corresponding Week 6, 18, 24, and 52 samples were assayed if they were also binding antibody positive. Neutralizing antibodies to AUX-I or AUX-II, were detected in 60% and 51.8%, respectively, of patients tested.

In patients treated for these two indications, there was no apparent correlation of antibody frequency, antibody titers, or neutralizing status to clinical response or adverse reactions.

Since the protein components in XIAFLEX (AUX-I and AUX-II) have some sequence homology with human matrix metalloproteinases (MMPs), anti-product antibodies could theoretically interfere with human MMPs. In vitro studies showed no evidence of cross-reactivity between anti-drug-antibody positive patient sera and a series of relevant MMPs. In addition, no clinical safety concerns related to the inhibition of endogenous MMPs have been observed.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to collagenase clostridium histolyticum with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

Anticoagulant drugs: XIAFLEX should be used with caution in patients receiving concomitant anticoagulants (except for low-dose aspirin) *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of XIAFLEX in pregnant women. Because animal reproduction studies are not always predictive of human response, XIAFLEX should be used during pregnancy only if clearly needed.

Risk Summary

Based on animal data, XIAFLEX is not predicted to increase the risk for major developmental abnormalities in humans.

Human Data

Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection into a Dupuytren's cord.

Low levels of XIAFLEX were quantifiable in the plasma of evaluable male subjects for up to 30 minutes following administration of XIAFLEX into the penile plaque of subjects with Peyronie's disease *[see Clinical Pharmacology in the full Prescribing Information]*.

Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical significance of anti-product antibody formation on a developing fetus is not known *[see Adverse Reactions]*.

Animal Data

Reproduction studies have been performed in rats with intravenous exposures up to approximately 11 times the maximum recommended human dose (MRHD) of XIAFLEX on a mg/m^2 basis, and have revealed no evidence of impaired fertility or harm to the fetus due to collagenase clostridium histolyticum.

Nursing Mothers

It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XIAFLEX is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of XIAFLEX in pediatric patients less than 18 years old have not been established.

Geriatric Use

Of the 551 XIAFLEX-treated patients in the double-blind, placebo-controlled, clinical trials in Peyronie's disease (Studies 1 and 2), 100 (18%) were 65 years of age or older and 5 (0.9 %) were 75 years of age or older. No overall differences in safety or effectiveness of XIAFLEX were observed between these patients and younger patients.

OVERDOSAGE

The effects of overdose of XIAFLEX are unknown. It is possible that multiple simultaneous or excessive doses of XIAFLEX may cause more severe local effects than the recommended doses including serious adverse reactions in the injected area (e.g., tendon ruptures or corporal ruptures dependent on the injection site). Supportive care and symptomatic treatment are recommended in these circumstances.

Manufactured and distributed by:
Auxilium Pharmaceuticals, Inc.
Chesterbrook, PA 19087

This Brief Summary is based on PL-0108-001.e
Revised 12/2013

CLINICS

continued from page 43

Dr. Wessells says the men's center there has exceeded expectations in number of visits.

"We're bringing in new business to the department and to the university," Dr. Wessells said. "It's a successful model."

While each of these clinics has been financially successful, according to those we interviewed, garnering patients takes marketing and outreach, Dr. Hotaling says.

"Most of your patients are not coming in from referrals because men don't see doctors," he said. "So we have a pretty good marketing team that helps us do outreach on the Web and on the news. We're trying to differentiate ourselves, mainly saying that we can offer comprehensive care, with this as a portal entry. No matter what your urologic or other issue is, we have a team of experts in place to address it."

One of the pillars of UW Medicine's marketing approach was to provide outreach and education, and garner community input, according to Dr. Walsh.

"We did this a number of different ways. We delivered community health talks that were supported by the men's health center, where we would bring men in to learn about their conditions," Dr. Walsh said. "We also did things that were a little more complicated and have really been beneficial. For example, we have assembled a community advisory board for men's health. Among these men, some had men's health conditions, but others were simply community leaders. We asked them: What should we be doing? What would you want to see in a men's health center? What services should we offer? How should we do outreach?"

MORE ABOUT MEN'S HEALTH ONLINE

For additional content regarding men's health, visit *bitly.com/UT-mens-centers,* where you'll find:

- Slideshow "tours" of several of the men's health centers profiled in this article
- Blog: Five must-haves for a successful men's health center
- Blog: Key design elements for men's health clinics
- "Men's health: The argument for a holistic approach," by Steven A. Kaplan, MD
- The inaugural edition of 'Y' tube, a compilation of men's health videos curated by University of Utah urologist James M. Hotaling, MD, MS
- The AUA's Men's Health Checklist, designed as a resource of urologic and non-urologic men's health considerations and to better coordinate their care between providers.

Artwork is on display in an exam room at the Preston Robert Tisch Center for Men's Health at NYU Langone Medical Center. (Photo courtesy of Rene Perez/NYU)

Not all centers have the financial backing to do full-blown marketing campaigns. That's not a problem, according to Dr. Miner.

"Based on the hospital's figures, we're now moving to net receipts (this is different than charges because you get about 50% of your receipts), and we've grown in numbers. We have had little marketing at all. It's largely word of mouth," Dr. Miner said.

According to Dr. Miner, half of The Miriam Hospital center's patients are self-referred. The others are the result of grand rounds that Dr. Miner and another physician from the center give to different departments—cardiology, pulmonology, infectious disease, psychiatry, and general internal medicine—about once every 2 years.

"It's a philosophy that we think beyond our own specialties."

STEVEN A. KAPLAN, MD

"Patients are referred from within. They come to us for a short period of time—about three visits. Then, they're referred back to their primary care physician always with evaluation and recommendations for their care, including their sexual dysfunction. This includes increased management of their risk factors for cardiovascular disease, including diet," Dr. Miner said.

Words of wisdom

Urologists and other physicians should see how the concept of a men's health center fits into their individual health care environments—whether those are hospitals, academic centers, or multispecialty groups, Dr. Wessells said.

"For example, when we started talking about this, there were primary care physicians who were worried that we were going to take business from them. So I think you need to understand the context you're working in and how best to collaborate," Dr. Wessells said.

It is important to refer back to the community primary care physicians, according to Dr. Miner.

"The biggest threat that we had when we started the center was not from urologists, because they know that they don't know medicine, frankly," he said. "The biggest threat was, what value do we add to the primary care clinicians in helping co-manage their patients? They may feel that they do just fine. But they honestly don't have the time to sit down and spend an additional 40 minutes for an evaluation of a patient with sexual dysfunction or low testosterone."

The big picture: Gender branding

Dr. Kaplan said that he often gets calls from others around the country who want to build comprehensive men's health centers. The men's health brand is growing. Health centers, private practitioners and groups, and academic centers that capitalize on gender-specific medicine will win because patients will demand it, according to Dr. Kaplan.

"I think it's great because it's a statement that men matter," Dr. Lamm said.

For the brand to continue successfully, however, it will require that more clinicians become trained in men's health, according to Dr. Miner.

"Finding an internist or a person with knowledge in medicine, whether that's a cardiologist or an endocrinologist, who is willing to learn about urology is rare. I was trained as a family physician, but I belong to the AUA and the Sexual Medicine Society of North America. I've been on the board of the SMSNA. There are very few non-urologists who achieve that," Dr. Miner said. "If we want this kind of model to continue, we have to have a fellowship in male andrology or broader men's health, so we can train younger physicians in this field. Right now the only fellowship in men's health that exists is for urologists." UT

October 2014

20-24
International Continence Society Annual Meeting
RIO DE JANEIRO, BRAZIL
Email: info@icsoffice.org
www.ics.org

23
Small Renal Mass 360°: An AUA Surgical Summit
MULTIPLE LOCATIONS
Tel: 800-908-9414
Email: registration@AUAnet.org
www.auanet.org

23-24
International Pelvic Pain Society Annual Meeting
CHICAGO
Tel: 847-517-8712
Email: info@pelvicpain.org
www.pelvicpain.org

24-26
Pediatric Urology Fall Congress
MIAMI BEACH, FL
Tel: 978-927-8330
www.spuonline.org

26-30
American College of Surgeons Clinical Congress
SAN FRANCISCO
Tel: 312-202-5000 or 800-621-4111
Email: postmaster@facs.org
www.facs.org

26-31
Western Section of the AUA Annual Meeting
MAUI, HI
Tel: 714-550-9155
Fax: 714-550-9234
Email: Info@wsaua.org
www.wsaua.org

31-Nov. 3
Society of Urologic Nurses and Associates Annual Conference
LAKE BUENA VISTA, FL
Tel: 888.827.7862
Email: suna@ajj.com
www.suna.org

STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION
(Requester Publications Only)
(Required by 39 USC 3685)

1.	**Publication Title:** Urology Times		
2.	**Publication Number:** 0093-9722		
3.	**Filing Date:** 9/30/14		
4.	**Issue Frequency:** Monthly, except two issues in April		
5.	**Number of Issues Published Annually:** 13		
6.	**Annual Subscription Price (if any):** $99.00		
7.	**Complete Mailing Address of Known Office of Publication:** 131 West First Street, Duluth, St. Louis County, Minnesota 55802-2065 **Contact Person: Wendy Bong Telephone: 218-740-7244**		
8.	**Complete Mailing Address of Headquarters or General Business Office of Publisher:** 2501 Colorado Avenue, Suite 280, Santa Monica, CA 90404		
9.	**Full Names and Complete Mailing Addresses of Publisher:** Samantha Armstrong, 485F US Hwy 1S, Suite 210, Iselin, NJ 08830 **Group Content Director:** Richard R. Kerr, 24950 Country Club Blvd, North Olmsted, OH 44070 **Content Specialist:** Benjamin P. Saylor, 24950 Country Club Blvd, North Olmsted, OH 44070		
10.	**This publication is owned by:** Advanstar Communications Inc., 2501 Colorado Avenue, Suite 280, Santa Monica, CA 90404. The sole shareholder of Advanstar Communications Inc. is: Advanstar, Inc., whose mailing address is 2501 Colorado Avenue, Suite 280, Santa Monica, CA 90404.		
11.	**Advanstar Communications Inc. is a borrower under Credit Agreements dated June 6, 2013, with various lenders as named therein from time to time. As of August 7, 2014, the agent for the lenders is: Goldman Sachs Lending Partners LLC, Administrative Agent, 30 Hudson St, 4th Floor, Jersey City, NJ 07302.**		
12.	**Does Not Apply**		
13.	**Publication Title:** Urology Times		
14.	**Issue Date for Circulation Data Below:** August 2014		
15.	**Extent and Nature of Circulation**	**Average No. Copies Each Issue During Preceding 12 Months**	**No. Copies of Single Issue Published Nearest to Filing Date**
	A. Total Number of Copies	**11,671**	**11,562**
	B. Legitimate Paid and/or Requested Distribution		
	1. Outside County Paid/Requested Mail Subscriptions Stated on PS Form 3541	**5,725**	**6,235**
	2. In-County Paid/Requested Mail Subscriptions Stated on PS Form 3541	**0**	**0**
	3. Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS	**31**	**35**
	4. Requested Copies Distributed by Other Mail Classes Through the USPS	**0**	**0**
	C. Total Paid and /or Requested Circulation (Sum of 15b (1), (2), (3), and (4))	**5,756**	**6,270**
	D. Non-requested Distribution		
	1. Outside County Non-requested Copies Stated on PS Form 3541	**5,530**	**5,022**
	2. In-County Non-requested Copies Stated on PS Form 3541	**0**	**0**
	3. Non-requested Copies Distributed Through the USPS by Other Classes of Mail	**0**	**0**
	4. Non-requested Copies Distributed Outside the Mail	**212**	**249**
	E. Total Non-requested Distribution (Sum of 15d (1), (2), (3) and (4))	**5,743**	**5,271**
	F. Total Distribution (Sum of 15c and e)	**11,499**	**11,541**
	G. Copies not Distributed	**172**	**21**
	H. Total (Sum of 15f and g)	**11,671**	**11,562**
	I. Percent Paid and/or Requested Circulation	**50.06%**	**54.33%**
16.	**Electronic Copy Circulation** *If you are not claiming electronic copies, skip to line 17		
	a. Requested and Paid Electronic Copies		
	b. Total Requested and Paid Print Copies (Line 15C) + Requested/Paid Electronic Copies		
	c. Total Requested Copy Distribution (Line 15F) + Requested/Paid Electronic Copies		
	d. Percent Paid and/or Requested Circulation (Both Print & Electronic Copies)		
	☐ I certify that 50% of all my distributed copies (electronic and print) are legitimate requests or paid copies.		
17.	**Publication of Statement of Ownership for a Requester Publication is required and will be printed in the October issue of this publication.** **Name and Title of Editor, Publisher, Business Manager, or Owner:** Christine Shappell, Audience Development Director **Date:** 9/30/14 *I certify that the statements made by me above are correct and complete.*		

Advertisers Index

Companies featured in this issue

To obtain additional information about products advertised in this issue, use the contact information below. (Regional ads are marked with an asterisk.) *This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.*

Advertiser Name	Brand/Product	Page #	Website
Accurate Surgical & Scientific Instruments	Noble Non-stick Forceps	21	www.accuratesurgical.com
American Medical Systems	AMS 700	31	www.AmericanMedicalSystems.com
Amgen	XGEVA	26-29	www.xgeva.com
Astellas	XTANDI	16-19	www.xtandihcp.com
Auxilium Pharmaceuticals	XIAFLEX Peyronie's Disease	44-46	www.askaboutthecurve.com
Bayer HealthCare Pharmaceuticals	Xofigo	Covertip*	www.xofigo-us.com
Cook Medical	Ureteroscopy, Flexor Vue & VueLite	23, 25	www.cookmedical.com
Endo Pharmaceuticals	AVEED	Outsert*	www.endo.com
Genentech	Immunotherapy-Bladder Clinical Trial	7	www.gene.com
Genomic Health	Oncotype DX	13	www.OncotypeDX.com/GPS
Janssen Biotech	ZYTIGA	33-38	www.zytigahcp.com
Myriad Genetics	Prolaris	CV4	www.myriad.com
Olympus America	Thunderbeat	9	www.OlympusThunderbeat.com
Pfizer	Viagra	CV2-5	www.viagra.com
Physician Reimbursement Systems	–	42	www.prsnetwork.com

UROLOGY TIMES (ISSN 0093-9722 PRINT), (ISSN 2150-7384 DIGITAL) is published 13 times a year: monthly with 2 issues in April by Advanstar Communications Inc., 131 W First St., Duluth MN 55802-2065. Subscription rates: $99 for 1 year in the United States and Possessions; $147 for 1 year in Canada and Mexico; all other countries $195 for 1 year. Price includes air-expedited service. Single copies (prepaid only): $13 in the United States; $18 in Canada and Mexico; $22 all other countries. Include $6.50 per order plus $2 per additional copy for U.S. postage and handling. If shipping outside the U.S., include an additional $25 per order plus $5 per additional copy. **Periodicals postage paid** at Duluth MN 55806 and additional mailing offices. **POSTMASTER:** Address changes, P.O. returns, etc. should be forwarded to Urology Times, c/o Advanstar Communications, Inc., P.O. Box 6021, Duluth, MN 55806-6021. Canadian GST number: R-124213133RT001, PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA.

Products & Services

EQUIPMENT FOR SALE

INSTRUMENTS

Recruitment

TENNESSEE

‘Open Payments’ moves forward despite snags

Disclosures set to go public Jan. 1; AUA, others call for delay

Bob Gatty
UT Washington Correspondent

Bob Gatty, a former congressional aide, covers news from Washington for *Urology Times*.

Washington—Physicians, including urologists, now have another headache to deal with—making certain information about them published on the Internet by the federal government is accurate and not misleading to patients who want to know about the financial benefits their doctors receive from manufacturers of drugs, devices, and biologic and medical supplies.

It’s all part of the National Physician Payment Transparency Program (Open Payments) established by the Affordable Care Act (ACA), which requires manufacturers to collect data on payments or items of value given to teaching hospitals and physicians. Manufacturers must also report certain ownership or investment interests by physicians or their immediate family members held at any point during the reporting year.

The website containing the data reported by manufacturers was slated to go live on Sept. 30, when the Centers for Medicare & Medicaid Services would make public details about provider payments made from Aug. 1, 2013 to Dec. 31, 2013. Physicians and teaching hospitals had until Sept. 8 to sign up, review their records, and dispute any discrepancy.

Tech issues hamper program

The Open Payments program has been plagued with delays and technical snafus. CMS took the system offline Aug. 3 to resolve a technical issue, and it was not restored until Aug. 15. According to CMS, an investigation into a physician complaint found that manufacturers and group purchasing organizations (GPOs) submitted intermingled data, such as the wrong state license number or national provider identifier for physicians with the same last and first names.

“[CMS] has not provided effective notification to the vast majority of physicians nor provided a reasonable amount of time for the undersigned organizations to engage and educate physicians on the registration and dispute process.”

MEDICAL GROUPS’ LETTER TO CMS

On Aug. 15, CMS said it has resolved the issue and revalidated all data to make sure physician identifiers used by the applicable manufacturer or GPOs are accurate. Incorrect payment transactions were removed and will not be published, CMS added.

Going forward, the ACA requires manufacturers to report the information annually to CMS by June 30 of each year. So physicians who want to make sure the data about them is accurate must be vigilant and check it within CMS guidelines.

According to CMS, physicians are not required to register with or send any information to Open Payments. However, to make sure CMS has correct information, physicians are encouraged to keep records of all payments and other transfers of value received from manufacturers or GPOs, register with the program, subscribe to its listserv, look at the applicable information, and make sure the information submitted about them is correct.

A group of more than 100 national and state medical organizations, including the AUA and the Large Urology Group Practice Association (LUGPA), sent a letter Aug. 5 to CMS Administrator Marilyn Tavenner urging that information collected so far not be made public until March 31, 2015. They said the extra time was needed because the opportunity for physicians to register had been delayed for 6 months after the original Jan. 1 target date.

“The agency has not provided effective notification to the vast majority of physicians nor provided a reasonable amount of time for the undersigned organizations to engage and educate physicians on the registration and dispute process,” the letter declared. “Early in the regulatory process, medicine informed CMS that a minimum of 6 months would be needed to ensure an adequate amount of time for outreach on registration and the dispute process.”

In addition, the medical groups noted that “many physicians are expressing frustration at an overly complex registration process which, combined with the condensed time frame, makes the task of reviewing and disputing reports by Aug. 27 effectively impossible for the agency’s estimated 224,000 covered physician recipients.”

A similar letter was sent to Tavenner July 28 by the Alliance of Specialty Medicine, of which the AUA is a member.

AUA: Industry-doc relationships ‘integral’

Meanwhile, in an online fact sheet regarding the program, the AUA notes that the reports “will provide increased transparency about financial relationships between biopharmaceutical companies, device manufacturers, and health care providers. The AUA also points out that the collaboration between physicians and biopharmaceutical companies in research is “integral” in finding breakthrough treatments for patients.

The AUA adds that manufacturers play a key role in sharing accurate, up-to-date information on new drugs and technologies with physicians, which helps them stay current on the newest treatments available.

“The AUA supports the principles of the Physician Payments Sunshine Act and transparency between physicians and industry,” the fact sheet states. “We are committed to providing meaningful background about ways in which physicians and the biopharmaceutical industry collaborate for patients.” UT

Fast Facts

The National Physician Payment Transparency Program (Open Payments):

- requires manufacturers to collect data on payments or items of value given to teaching hospitals and physicians
- requires manufacturers to report information annually to CMS by June 30 of each year going forward
- has been plagued with delays and technical snafus, including a situation in which manufacturers and group purchasing organizations submitted intermingled data
- is set to make collected information public on Jan. 1, 2015, although the AUA and others are calling for a delay until March 31

Feedback Send your comments to Bob Gatty c/o *Urology Times*, at **UT@advanstar.com**

IN THE PUBLIC Eye

WHAT YOUR PATIENTS ARE READING IN PRINT, ONLINE

FOXNEWS.COM

Tomato-rich diet associated with decreased risk of prostate cancer

TOMATO CONSUMPTION may lower the risk of prostate cancer by nearly 20%, British researchers recently reported.

For the study, which was published online in *Cancer Epidemiology, Biomarkers and Prevention* (July 13, 2014), the authors assessed diets and lifestyles of 1,806 prostate cancer patients between the ages of 50 and 69 years and compared them to 12,005 cancer-free men.

18%
DECLINE IN PCA RISK IN MEN EATING >10 TOMATO SERVINGS PER WEEK

The researchers, led by Vanessa Er, PhD, of the School of Social and Community Medicine at the University of Bristol, Bristol, United Kingdom, found that men who ate more than 10 servings of tomatoes per week reduced their risk of prostate cancer by 18%. The authors say they believe this decreased risk may be attributed to the antioxidant lycopene contained in tomatoes.

CNN.COM

'Black box' may help monitor surgeon performance in the OR

CANADIAN RESEARCHERS are working on a surgical tracking box—similar to black boxes used in airplanes—that records surgeons' movements and identifies errors during an operation.

Video cameras would track movements inside the operating room while a small, computer-like device outside the OR analyzes the recordings, identifies mistakes, and provides instant feedback to surgeons as they operate.

By pinpointing mistakes and letting a surgeon know if he/she is veering off course, this black box could prevent mistakes, said Teodor Grantcharov, MD, PhD, of St. Michael's Hospital, Toronto.

Unlike airplane black boxes, which are used after a disaster, these would be used proactively to prevent complications.

However, there are concerns that if recordings were used in court, it could create new malpractice problems.

NEWYORKTIMES.COM

Report: High number of independent seniors live with incontinence

THIRTY-SEVEN MILLION SENIORS who live independently have some type of incontinence, according to research published in *Vital Health Statistics* (2014; 36:1-33).

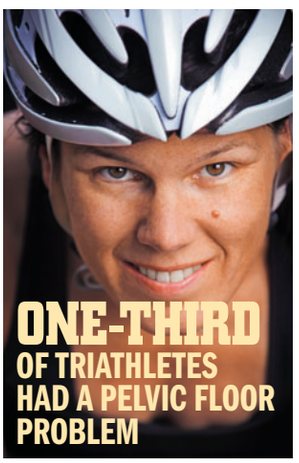
"This presents a significant financial and emotional burden to the individual and society," said first author Yelena Gorina, MS, MPH, of the National Center for Health Statistics, Washington.

Urinary leakage was the most common form of incontinence reported, affecting four out of 10 seniors. While many cases were mild, 24% of older adults reported moderate or severe urinary incontinence warranting medical attention.

MILITARYTIMES.COM

Female triathletes may be at risk for pelvic floor problems

FEMALE TRIATHLETES are at risk for developing pelvic floor conditions such as incontinence or prolapse, according to a study presented at the American Urogynecologic Society annual scientific meeting in Washington.



Researchers at Loyola University Health System, Maywood, IL, found that about one-third of 311 female athletes suffered from incontinence or some other pelvic floor problem.

The study did not establish a causal link between training and pelvic issues. Researchers Colleen Fitzgerald, MD, and Johnny Yi, MD, said the miles and intensity of their training did not appear to give them increased risk compared with other females.

PHOTOS: GETTY IMAGES / TOMATOES: ALEXLUKIN / WOMAN: JOHNER IMAGES

JOIN THE CONVERSATION ON facebook.com/urologytimes or twitter.com/urologytimes

News Oddities

'Robotic sperm' promising for fertilization, chemo

A TINY, SPERM-LIKE ROBOT could have potential for both fertilization and cancer treatment, researchers from the American Institute of Physics, College Park, MD, reported online in *Applied Physics Letters* (June 2, 2014).

The "MagnetoSperm" are approximately six times longer than a human sperm. They are controlled with a weak magnetic field. Like real sperm, they flip their tails to swim toward their target. But unlike real sperm, they are made of a metal-coated polymer.

The authors also speculate that MagnetoSperm could help to improve egg fertilization because it's "designed to move very, very small things around." The robots could be used to assemble any object on nano- and micro-scales, according to an article on the VentureBeat website.

In addition, the sperm-like robots may benefit patients who undergo chemotherapy that damages healthy cells during treatment. Physicians could use the robots to more accurately target cancer cells, and could help protect healthy cells from exposure.

ACTIVE SURVEILLANCE OR INTERVENTION?

The choice is clearer when you reveal prostate cancer's true nature.

Prolaris® combines traditional risk factors with a molecular assessment of the aggressiveness of an individual patient's cancer to deliver a prostate cancer-specific 10-year mortality risk. So you and your patient can make a more confident, more personalized decision when choosing between intervention and active surveillance.

To find out more, call Myriad at 855.469.7765 or visit prolaris.com

Prolaris®
Truly Revealing

MYRIAD