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ICD-10: What you don't know might hurt you

Failure to understand new codes may jeopardize physicians' pay

Lisette Hilton | UT CORRESPONDENT

National Report—Urologists know the International Classification of Diseases-10 (ICD-10) goes into effect Oct. 1, 2015. Whether they understand the transition's impact and what they need to do to fully prepare are questionable.

Mark Painter, CEO of Denver-based PRS Urology, says many larger practices are on track for the transition from ICD-9 to ICD-10. However, there are also many urology practices (primarily small- and medium-sized practices) that are nowhere close to where they need to be in less than a year.

"There are many folks who haven't done system updates or testing and haven't really begun full-on training," Painter told *Urology Times*.

Painter says there's still time, but the time to start readiness campaigns for ICD-10 is now. Practices need to establish champions or groups in charge of overseeing the transition, start staff and physician training in April 2015, and be ready to test when testing opportunities become available. Only 36% of urology practices have taken the early step of putting someone in charge of overseeing the transition, according to an informal survey conducted on UrologyTimes.com last month.

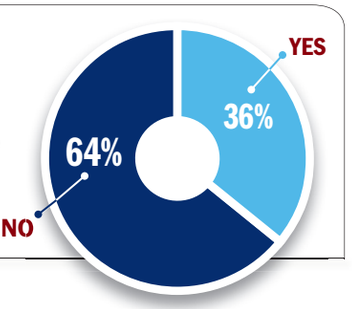
Barring a third delay, urology and other practices will have no time to ease into the new system. They'll go from using ICD-9 on Sept. 30, 2015 to starting the next day with ICD-10. And what urologists and their practices don't know about ICD-10 starting Oct. 1 could hurt them financially.

Jonathan Rubenstein, MD, a urologist in Baltimore and member of the AUA's Coding and Reimbursement Committee, is among those who represents the AUA at the government's ICD-10 Coordination and Maintenance Committee meetings. He says ICD-10 is going to dramatically

Please see **PREPARE,** on page 38

UT asks

Has your practice put someone in charge of overseeing ICD-10?



Source: *Urology Times* October 2014 online survey

ICD-10: THE COSTS TO PREPARE

COST AREA	TYPICAL SMALL PRACTICE	TYPICAL MEDIUM PRACTICE	TYPICAL LARGE PRACTICE
Vendor/software upgrades	$0–$60,000	$0–$200,000	$0–$2,000,000
Testing	$15,248–$28,805	$47,906–$93,098	$428,740–$880,660
Payment disruption	$22,579–$100,349	$75,263–$334,498	$752,630–$3,344,976
Other*	$18,812–$36,951	$90,195–$197,139	$835,781–$1,792,728
TOTAL COSTS	$56,639–$226,105	$213,364–$824,735	$2,017,151–$8,018,364

*Other costs relate to training, assessment, process remediation, and productivity loss

Source: American Medical Association

Inside THIS ISSUE

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Q&A
WORKPLACE SAFETY
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Dr. Rhee discusses challenges to safeguarding practices. **See page 23.**

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Clinical Updates

Business of Urology

Departments

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.

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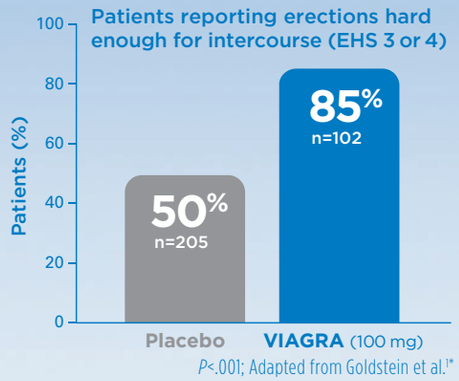
Pfizer U.S. Pharmaceuticals

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)*].

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NOVEMBER 2014 VOL. 41, NO. 12
The Leading News Source for Urologists
UrologyTimes.com

Pre-chemo Tx: More ammo for urologists

The recent report of the final analysis of COU-AA-302 at the 2014 European Society of Medical Oncology Congress adds another weapon in the armamentarium in the fight against metastatic, castration-resistant prostate cancer.

Ryan et al reported overall survival and safety outcomes in 1,088 patients randomized to abiraterone acetate (ZYTIGA), 1,000 mg, plus oral prednisone, 5 mg twice daily, versus prednisone plus placebo with a medium follow-up of 49.4 months (see page 9). Patients in the placebo arm were allowed to cross over to the treatment arm, and 44% ultimately received abiraterone after unblinding. Abiraterone plus prednisone significantly prolonged overall survival versus prednisone alone (34.7 vs. 30.3 months).

J. Brantley Thrasher, MD

Dr. Thrasher, a *Urology Times* editorial consultant, is professor and chair of urology, University of Kansas Medical Center, Kansas City.

Adverse events were infrequent, with grade 3/4 hypertension in 4.6% of patients, hypokalemia (2.6%), increase in ALT (5.9%), and increase in AST (3.3%).

This is the second drug in recent months to show significant improvement in overall survival in chemotherapy-naïve patients. Data from PREVAIL, the phase III trial of enzalutamide (XTANDI), showed that agent significantly reduced the risk of radiographic progression or death by 83% versus placebo.

The time is right for urologists to become familiar with all aspects of the use and delivery of these drugs.

Chemo-naive patients routinely start out in the urologist's office, but many practices elicit the aid of their medical oncology colleagues following failure of androgen deprivation therapy. We now have a second drug with a very favorable safety profile, ease of delivery, and a familiar mechanism of action for the urologist. The time is right for urologists to become familiar with all aspects of the use and delivery of these drugs.

Further, the current data lead the way for many more interesting studies in the patient with metastatic prostate cancer. It certainly appears that earlier delivery of abiraterone is beneficial, but how early? What will be the best sequencing of these new agents? Will combination therapy prove superior to single-drug therapy?

These are exciting times for those who treat advanced prostate cancer, but with so many new weapons, the time is now for urologists to engage in their use and continue to research the best sequence of delivery.

J. Brantley Thrasher, MD

Feedback

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

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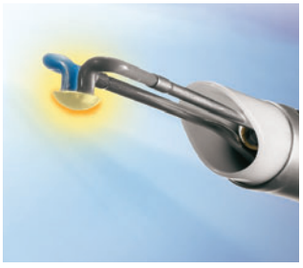

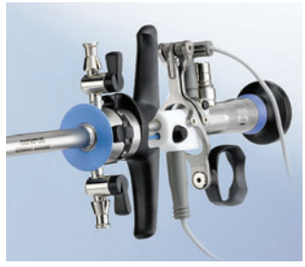

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AACU LEGISLATIVE UPDATE

Pressure to expand Medicaid mounts, employer plans decline

When provisions of the Affordable Care Act related to the expansion of Medicaid to low-income childless adults took effect in January 2014, 25 states and the District of Columbia had approved laws to broaden their programs' eligibility requirements. Since then, under pressure from various interest groups, including state hospital associations, lawmakers in a handful of states expanded their health care safety net programs and thereby gained access to federal dollars that would have otherwise been left on the table. Arkansas, Iowa, Michigan, and Pennsylvania are leading the way in the pursuit of a so-called "private option."

READ ABOUT STATES' MEDICAID EXPANSION PLANS AT: *bitly.com/Medicaid-expansion*

BLOG

One urologist's lessons from 'Googling' himself

DR. ROSEVEAR

Have you ever "Googled" yourself? If you haven't, try it. The results may surprise you. Not all of it is pretty, says urologist Henry Rosevear, MD. However, as Dr. Rosevear explains in his most recent *Urology Times* blog, there are ways to manage your own online reputation and that of your group. One solution is to hire a company to take ownership of online reviews, the cost of which Dr. Rosevear says is easily recouped with just a few new patients.

LEARN FROM DR. ROSEVEAR'S EXPERIENCE AT: *bitly.com/Rosevear-googling*

UT FOLLOWER OF THE MONTH

@drchrisdiblasio

Christopher DiBlasio, MD, a Huntington, NY urologist, is the *Urology Times* Twitter follower of the month! To be featured in this section, engage with us. TWITTER.COM/UROLOGYTIMES

Urologists, others tackle prostate Ca on AUA 'UroChat'

Matthew Cooperberg, MD
@dr_coops
One clear bottom line: if we do not fix overtreatment, we will never retake the terms of the screening debate. *#AUAUroChat @AmerUrological*

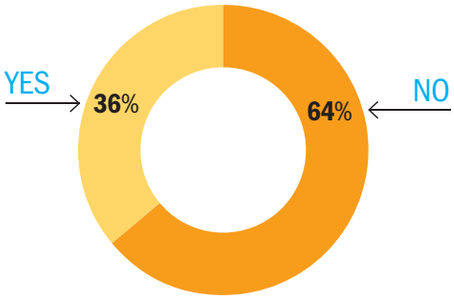
Stacy Loeb, MD
@LoebStacy
@DrRKSingal @AmerUrological @scientistatlrge Since no test is perfect,combining risk factors together for decisions is judicious *#AUAUroChat*

David Canes
@CanesDavid
.@AmerUrological @lucianadisraeli Don't throw baby out w/the bathwater. Active surveillance is the answer to the PSA debacle. *#AUAUroChat*

Mike Haynes
@MikeHaynesNFL
.@AmerUrological - My grandfather had *#ProstateCancer*. Didn't know I was considered high risk because of it - *@KnowYourStats #AUAUroChat*

OCTOBER'S QUESTION OF THE MONTH

Have you put someone in charge of overseeing ICD-10?



QUESTION FOR NOVEMBER

Should CT be the initial imaging test in patients with colicky flank pain?

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Second mCRPC agent shows significant benefit pre-chemo

Abiraterone improves overall survival, time to opiate use in phase III study

Wayne Kuznar
UT CORRESPONDENT

Madrid, Spain—Abiraterone acetate (ZYTIGA) as therapy for chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) improved overall survival by a statistically significant 19% compared with placebo in the final analysis of the phase III COU-AA-302 clinical trial.

Prostate Cancer

The study data importantly address "the very important question of the timing of this agent" and the benefit of earlier treatment, according to one prostate cancer expert.

Dr. Ryan

The final analysis, presented at the European Society of Medical Oncology annual meeting in Madrid, Spain, consisted of data from 49.2 months of follow-up. A third interim analysis had already shown a doubling in the time to radiographic progression-free survival (rPFS), from 8.2 months in the placebo/prednisone arm to 16.5 months in the abiraterone/prednisone arm (p<.0001). The benefit on overall survival with abiraterone did not meet the required p-value for significance at the three interim analyses but did so at the time of the final analysis, reported lead investigator Charles J. Ryan, MD, associate professor of medicine and urology at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.

Abiraterone is the second agent for mCRPC to show a significant survival benefit in the pre-chemotherapy setting. The FDA approved enzalutamide (XTANDI) in September based primarily on phase III study data showing enzalutamide significantly reduced the risk of death by 29% compared with placebo (HR: 0.71; p<.0001).

In the COU-AA-302 trial investigating abiraterone, eligible patients were required to have mCRPC and to be free of disease-related symptoms that would lead to a requirement for opiate analgesic use. The study included 1,008 men with mCRPC who were randomized to receive abiraterone, 1,000 mg orally once daily, with concurrent prednisone, 5 mg twice daily, or placebo plus prednisone, 5 mg twice daily.

The study was unblinded upon the recommendation of the Independent Data Safety Monitoring Committee after the second interim analysis based on a significant difference in rPFS as well as an emerging trend for OS in favor of abiraterone. After unblinding, the study was not discontinued. A subsequent protocol amendment allowed patients in the placebo arm to receive abiraterone.

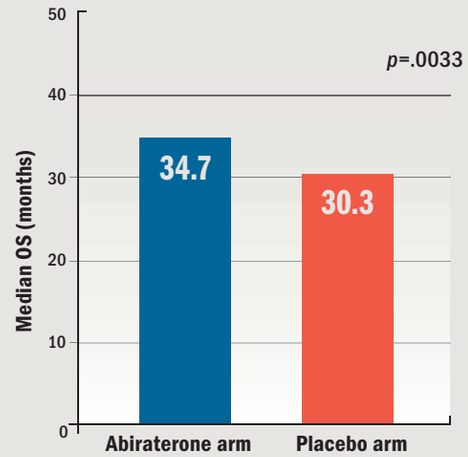
19% relative reduction in death risk

At the time of the final analysis, 92% of patients in the abiraterone arm and 100% in the placebo arm have discontinued therapy, most often for radiographic progression. Median OS was 34.7 months in the abiraterone arm and 30.3 months in the placebo arm, corresponding to a 19% relative reduction in the risk of death (p=.0033). The treatment effect of abiraterone was more pronounced when adjusting for the 44% of patients in the placebo group who subsequently received abiraterone (HR: 0.74).

More than one fourth of patients randomized into the abiraterone arm have survived for 48 months or longer, Dr. Ryan noted.

"OS is particularly noteworthy in COU-AA-302, because 67% of men in the ZYTIGA plus prednisone arm and 80% in the control arm received subsequent therapy. This includes 44% of men in the control arm who subsequently received ZYTIGA plus prednisone," Dr. Ryan said in a news release from Janssen Research & Development, LLC, which sponsored the study. "The use of subsequent therapies did not impact the statistical significance between the ZYTIGA and control arms, and makes these results all the more compelling after adjusting for the crossover effect."

UT Figure Median overall survival: Abiraterone vs. placebo



Source: Charles J. Ryan, MD

The final analysis also demonstrated a significant improvement in median time to opiate use for cancer-related pain for abiraterone compared with placebo (median of 33.4 vs. 23.4 months, respectively; p=.00001). No new safety signals emerged despite the longer duration of therapy and follow-up compared with prior analyses.

The trial was more of a comparison between early and late hormone treatment strategies rather than one testing the utility of abiraterone pre-chemotherapy, said Bertrand Tombal, MD, PhD, who was not involved in the study.

"When you look at the second treatment and you notice that nearly 50% received abiraterone, the design of the trial has become early abiraterone versus late abiraterone in 50% of the patients," said Dr. Tombal, of Université Catholique de Louvain, Brussels, Belgium. "More than ever, it addresses the very important question of the timing of this agent and the benefit of an earlier timing on the patient. To me, that is the most important question."

Over the past 60 years, studies have demonstrated that earlier hormone therapy changes the dynamic of progression but does not result in a major improvement in overall survival, he said. To have the greatest impact on overall survival, hormone therapy needs to be combined with some form of local treatment.

Based on the results of the final analysis, Janssen said it has initiated regulatory submissions to relevant health authorities for a revision to the abiraterone label.

Dr. Ryan has received honoraria from Janssen. Three study co-authors are employees of the company. UT

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Post-op complication, readmission rates similar

RARP: 'Little clear benefit' compared to open surgery

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Montreal—Robot-assisted radical prostatectomy (RARP) is associated with a lower rate of blood transfusion and shorter length of stay compared to open surgery. However, the total first-year reimbursement is higher for RARP and there is no difference between the two procedures in the rate of postoperative complications or use of additional cancer treatment, according to an analysis of contemporary data from the Surveillance, Epidemiology, and End Results Medicare-linked database.

Robotics

The study was presented at the AUA annual meeting in Orlando, FL and was recently published in the *Journal of Clinical Oncology* (2014; 32:1419-26). It included 5,915 men operated on between October 2008 and December 2009, of whom 41% underwent open radical prostatectomy and 59% had RARP.

"RARP was rapidly adopted after its introduction and is currently the dominant technique for surgical treatment of localized prostate cancer in the U.S., accounting for more than 60% of radical prostatectomy procedures," said first author Giorgio Gandaglia, MD, clinical research fellow, University of Montreal Health Center, Cancer Prognostics and Health Outcomes Unit, Montreal.

"Although reports from single-institution series show better outcomes with RARP than with an open approach, our study offers a population-based analysis of outcomes at the community level. It confirms previous investigations showing RARP is associated with substantially higher costs, but the main message is that RARP appears to have little clear benefit compared to open surgery. Nevertheless, although our study was designed to limit any effect of the steep learning curve for the robotic technique, we cannot rule out that RARP will prove to have greater benefit at a later time post-adoption."

The men in both study groups had a mean age of about 69 years and were predominantly Caucasian (~82%). Compared to the open surgery group, men undergoing RARP had significantly worse disease features according to analyses of clinical stage and Gleason score, but the open group had higher proportions of men with preoperative PSA >10.0 ng/mL and categorized as having high-risk disease. There were also statistically significant differences between surgical groups in pelvic lymph node dissection status and nodal stage such that patients treated with the minimally invasive approach were less likely to receive a PLND and to have nodal involvement.

UT Table Open vs. robot-assisted RP: Complications, readmissions

	Open	Robot-assisted
30-day postoperative complication rate	23.8%	22.2%
90-day complication rate	28.9%	26.0%
30-day readmission rate	3.8%	3.9%
90-day readmission rate	5.9%	5.5%
Rate of additional therapy within 6 months' post-op	6.3%	3.6%
Rate of additional therapy over study period	12.9%	9.0%
Rate of heterologous blood transfusion	8.9%	1.9%
Median length of stay	2 days	1 day

Source: Giorgio Gandalgia, MD

No significant differences in complications

Comparisons between the open and RARP groups showed no significant differences in the 30-day or 90-day postoperative complication rates (23.8% vs. 22.2% and 28.9% vs. 26.0%) nor in the 30-day or 90-day readmission rates (3.8% vs. 3.9% and 5.9% vs. 5.5%). Within the first 6 months after surgery, 6.3% of men who underwent open surgery and 3.6% of men in the RARP group received additional cancer therapy with radiotherapy or androgen deprivation, and over the entire study period, the rates of additional cancer therapy in the open and RARP groups rose to 12.9% and 9.0%, respectively ($p<.001$ for both comparisons). Rates of heterologous blood transfusion were 8.9% in the open group and 1.9% in men having RARP, and median length of stay in the two groups was 2 days and 1 day, respectively ($p<.001$ for both comparisons).

In determining the relative odds of the outcome measures of interest, an instrumental variable analysis technique was used that limited possible biases related to the effect of confounding factors. Its results showed statistically significant differences between the two techniques persisted in first-year reimbursement and risks of having a heterologous blood transfusion and prolonged length of stay, but not in risk of needing additional cancer therapy. UT

Protective patch linked to erectile function recovery

90% of patients receiving membrane during robotic RP regain function at 3 months

Mac Overmyer
UT CONTRIBUTING EDITOR

Taipei, Taiwan—The application of dehydrated human amniotic membrane (dHAM) as a therapeutic patch covering the neurovascular bundle may have profound effects on the early recovery of erectile function in men undergoing nerve-sparing, robot-assisted laparoscopic radical prostatectomy, a retrospective study suggests.

The study examined 60 patients who underwent surgery for low-volume prostate cancer. Of 22 men receiving an AmnioFix (MiMedx, Marietta, GA) dHAM during a bilateral nerve-sparing procedure, 20 (90.9%) demonstrated a return of erectile function at 3 months, and 21 men (95.5%) recovered function at 6 months. In 38 men undergoing the same procedure but without the dHAM, 16 (42.1%) recovered erectile function at 3 months and 20 (52.6%) at 6 months ($p=.0005$ at 3 months and $\leq.0002$ at 6 months for the cohort comparisons).

The patch appears to assert its influence early. Only two of the men (5.26%) without the patch had erectile function at first follow-up compared to nine of men (40.9%) receiving the patch ($p=.0006$).

"I think we now have a means of circumventing some of the surgical trauma (associated with nerve-sparing prostatectomy). No matter how good we are, we inflict some trauma on these fine, delicate nerves," Sanjay Razdan, MD, MCh, director of the International Robotic Prostatectomy Institute and associate professor of urology at the Herbert Wertheim College of Medicine, Florida International University, Miami, told *Urology Times*.

"I think that adding this layer of protection with a dehydrated amniotic membrane is going to go a long way in bringing a rapid return of erectile function."

SANJAY RAZDAN, MD, MCH

Dr. Razdan, the study's lead author and sole surgeon, said the insults to the neurovascular bundle included thermal injury, inflammation, traction injury, and scar tissue formation.

"I think that adding this layer of protection with a dehydrated amniotic membrane is going to go a long way in bringing a rapid return of erectile function," he said.

Dr. Razdan explained that the dHAM derived its effects from a rich trove of growth factors such as TGF-a and TGF-b, which encourage wound healing; bFGF, which promotes cell growth and tissue repair; and factors such as EGF, PDGF, and VEGF, all of which mediate the proliferation and differentiation of cells. These factors have anti-inflammatory properties as well as anti-scarring effects.

Learning curve for procedure

Dr. Razdan said the procedure is not particularly challenging but that there is a definite learning curve.

"Once the prostatectomy is completed but before the urethral anastomosis is conducted, the membrane is passed to the site via a 12-mm side port," he explained. "My assistant rolls up the membrane, which is like parchment. It has to remain perfectly dry as it passes through the port because if it gets wet, you can't handle it. I grab it with the robotic arm and depending on the thickness and width of the neurovascular bundle, it can be placed as one sheet or if the bundles are wide apart, it can be cut into two sheets.

"It is wrapped around the nerve. The moment it gets moist, it sticks. There is no need for sutures. The sides are labeled 'up' and 'down.' The 'down' side goes onto the nerve. Otherwise, it will not stick."

The study was recognized as "The Best Paper in Robotics" following its presentation at the World Congress of Endourology and SWL in Taipei, Taiwan. The retrospective trial consisted of 22 dHAM patients and 38 controls with low-volume prostate cancer and good pre-procedure erections. Dr. Razdan conducted all procedures. The average age in the control group was 62 years (48-70) compared to 59 years (40-73) in the membrane group. Gleason scores for the controls were ≤6, 55%; 7, 45%; and 8-10, none. The Gleason scores for the membrane group were ≤ 6, 50%; 7, 36%; and 8-10, 14%. The mean International Index of Erectile Function score for the control group was 19.84 (SD, 3.02) compared to 20 (SD, 3.5) for the membrane group.

Given the responses seen in a pilot study, the WCE study, and initial data from a recently closed prospective randomized study, Dr. Razdan now offers the membrane to all patients who meet criteria of having low-volume disease and good preoperative erections. As might be expected, the costs of the procedure have yet to be covered by insurance.

One of the surprising aspects of the study may be that the membrane has not been used in prostatectomies earlier, said Dr. Razdan. He added that this is the first documented study in the world using dHAM during robotic prostatectomy. Dr. Razdan said he first learned of the membrane in a casual cafeteria conversation with a neurosurgeon. A subsequent literature search showed the membrane to have a well-established role in general, orthopedic, neurologic, podiatric, bariatric, and plastic surgeries.

Dr. Razdan received free membranes from MiMedx for the retrospective trial. UT

UTSTAT

Of men receiving a dHAM, 90.9% demonstrated a return of erectile function at 3 months, and **95.5% recovered function at 6 months.**

RARP checklist assesses, evaluates surgeon progress

Tool allows learning curves to be assigned to specific phases of procedure

Mac Overmyer
UT CONTRIBUTING EDITOR

Taipei, Taiwan—A new checklist-based assessment tool could prove to be useful for surgeons learning robot-assisted radical prostatectomy (RARP).

An international team headed by specialists in the urology department of King's College, London has been studying the learning processes that lead to proficiency in RARP and other urologic procedures for several years and has produced a number of studies on these subjects. At the World Congress of Endourology and SWL, the authors presented a study that deconstructs the procedure into constituent phases and gives each activity within a phase a difficulty rating that reflects the steepness of the learning curve required for competency. This most recent work created and subsequently validated a checklist that evaluates a surgeon's progress in acquiring proficiency with phases within the procedure and the procedure in its entirety.

"Essentially, the study had three aims. The first was to create a means of mapping the entire surgical procedure. The second is to create a training document for specific aspects of the procedure, and the third is to create a tool that will assess an individual's performance and provide feedback that has value," senior author Kamran Ahmed, PhD, MBBS, MRCS, special registrar in urology at King's College, told *Urology Times*.

The authors broke the procedure into 41 steps spanning 17 stages. In addition to defining each stage and step in the procedure, the study identified 84 "failure modes," 46 of which had a hazard score of 8 or greater, indicating that the failure could lead to significant adverse clinical events.

The study derived its approach to the procedure from the principles of the Failure Mode and Effect Analysis, a proactive system created by the military to identify potential failures and their causes, and to take preventive action.

"I suspect there is a technique for each and every surgeon. That is why we wanted a range of surgeons—to ensure that we captured every aspect of the procedure."

KAMRAN AHMED, PHD, MBBS, MRCS

The effort can be described as labor intensive. Key robotic prostatectomy steps were identified by watching five surgeons who logged 42 hours on the robot console.

Diverse team reviews process

Once the process was mapped in detail, it was reviewed by specialists from the UK, Europe, and the U.S. Dr. Ahmed explained that the diversity on the reviewing team was deliberate.

"There are so many techniques. I suspect there is a technique for each and every surgeon. That is why we wanted a range of surgeons—to ensure that we captured every aspect of the procedure," he told *Urology Times*.

A checklist of definitive tasks within each stage of the procedure was created, allowing each task to be evaluated by an observer as it was performed. Evaluations ranged from 1 (unacceptable) to 5 (excellent). This tool was then used to evaluate the progress of 17 surgical fellows from Europe, Asia, and Australia.

"There are characteristics of every education tool. It should be valid, reliable, feasible, acceptable, and should have an educational impact," said Dr. Ahmed. He added that he felt all these ends were accomplished in the tool he and his team created.

The observational data collected also allowed learning curves to be assigned to each phase of RARP, he noted.

"Most of the learning curves to date have been evaluations based on patient outcomes. It has never before been done this way because it can be a very tedious process," Dr. Ahmed said. The learning curve data allows focus to be placed on the more challenging aspects of RARP.

The authors noted that the steps involved in patient preparation were among the easier aspects of the procedure. Nerve sparing and vesico-urethral anastomosis were among the more challenging, Dr. Ahmed said.

The study was funded by the Royal College of Surgeons of England. UT

Robotic kidney transplant continues to show benefits

Blood loss, postoperative pain lower compared with open procedure

Mac Overmyer
UT CONTRIBUTING EDITOR

Taipei, Taiwan—An international team of surgeons from the U.S. and India continues to explore the potential of robotic kidney transplantation with regional hypothermia. The results of an IDEAL (Idea, Development, Exploration, Assessment, Long-term) phase IIb trial of the procedure support the promise seen in preceding trials.

"When we analyzed our data, we found that the patients who underwent a robotic kidney transplant had significantly lower analgesic requirements and that blood loss was significantly lower," first author Prasun Ghosh, MD, MBBS, MS, DNB, told *Urology Times*.

"There were no wound infections and there were no lymphoceles. These are substantial benefits seen in the robot arm," said Dr. Ghosh, senior consultant in urology and robotics and head of renal transplant at Medanta The Medicity Kidney & Urology Institute, Gurgaon, India.

"The low morbidity and comparable graft outcomes offered by this procedure may actually encourage chronic kidney disease patients to consider a preemptive transplant and subsequently reduce dialysis costs," he observed.

At the time of the presentation at the World Congress of Endourology and SWL in Taipei, Taiwan, patients had been followed for 6 months.

The prospective two-armed non-randomized trial consisted of 225 patients, 50 of whom underwent the robotic procedure and 175 of whom underwent the standard open procedure. Demographics in the two groups were similar. Mean age in the robot group was 37 years compared to 39 years in the open group. The majority of the patients were men, who constituted 75.9% of the robot group and 80% of the open group.

Origins of kidney failure included diabetes mellitus, hypertension, chronic glomerulonephritis, IgA nephropathy, interstitial nephritis, obstructive uropathy, and autosomal dominant polycystic kidney disease. There was one case of kidney failure of unknown origin in the robot arm and 12 such cases in the open group. The Charlson morbidity index was nearly the same in both arms—3.7 (SD, 2.1) in the robot arm and 3.2 (SD, 2.1) in the open arm.

OR time longer with robotic procedure

The operating time in the robotic procedure was significantly longer than in the open procedure, with a mean time of 201.1 minutes (range, 156-296 minutes) with the robot compared to a mean of 169.3 minutes in the open group (range, 105-263 minutes).

Ischemia times (IT) were slightly longer in the robot arm. In these patients, the mean warm IT was 2.3 minutes (range, 1.3-6.0 minutes), the mean cold IT was 27.7 minutes (range, 10-90 minutes), and mean re-warming IT was 42.9 minutes (range, 27-66 minutes) for a total mean IT of 73.1 minutes (range, 50.7-142.5 minutes).

In the open group, the mean warm IT was 2.4 minutes (range, 1.5-4.5), the mean cold IT was 19.4 minutes (range, 9.0-36.5), and mean re-warming IT was 31.3 minutes (range, 24.0-44.0) for a total mean IT of 53.1 minutes (range, 40.6-78.8), or roughly 20 minutes shorter than that of the robotic procedure.

"There is no doubt that the vascular anastomosis is the most challenging aspect of the robot procedure," said Dr. Ghosh.

Despite the challenge and length of the robotic procedure, blood loss was significantly lower. The median blood loss in the robot arm was 146.7 mL (range, 50-450 mL) compared to 345.6 mL (range, 100–1,200 mL) in the open group. Mean serum creatinine levels at discharge were 1.3 mg/dL in the robotic group and 1.2 mg/dL in the open group.

The mean incision length in the robot arm was 6.1 cm (range, 5.4-7.1 cm) compared to 15.1 cm (range, 13.4-16.2 cm) in the open procedure.

"We found the postoperative pain and analgesic requirements for those in the robot group were significantly lower than those who underwent the open procedure," Dr. Ghosh said.

As Dr. Ghosh noted, no lymphoceles were found in the robotic procedure patients on non-contrast computed tomography scans taken at 3 months post-op. Lymphoceles were detected in 42 patients (24%) undergoing the open procedure. The U.S. team was headed by Mani Menon, MD, of Henry Ford Hospital's Vattikuti Urology Institute, Detroit. UT

UT Table **Robotic vs. open renal transplantation**

	Robotic procedure	Open procedure
Mean OR time	201.1 min	169.3 min
Mean warm ischemia time	2.3 min	2.4 min
Mean cold ischemia time	27.7 min	19.4 min
Mean re-warming ischemia time	42.9 min	31.3 min
Total mean ischemia time	73.1 min	53.1 min
Median blood loss	146.7 mL	345.6 mL
Mean serum creatinine levels at discharge	1.3 mg/dL	1.2 mg/dL
Mean incision length	6.1 cm	15.1 cm

Source: Prasun Ghosh, MD, MBBS, MS, DNB

Alternatives to T therapy: Lessons from male infertility

Choice of three agents allows most men to transition from testosterone to alternative therapy

James M. Hotaling, MD, MS ● William O. Brant, MD

Testosterone use in the United States is currently rising at unprecedented levels. Annual testosterone prescriptions have increased more than five-fold from 2000 to 2011, resulting in $1.6 billion in revenue and 5.3 million testosterone prescriptions in 2011 alone (FDA Bone, Reproductive and Urologic Drugs Advisory Committee [*www.fda.gov*]; *Nature Rev Endocrinol* 2013; 9:414-24). Perhaps the best evidence of the success of testosterone therapy has been the recent Time cover article on "manopause" and the fact that the marketing campaign for "low T" is now taught at Harvard Business School as an example of the most successful marketing campaign in the history of medicine.

All of this has meant that urologists are now more than ever on the front lines of men's health. Both the desire to preserve the youthfulness of an aging baby boomer population and a younger population seeking a competitive edge in the work force—and in play—drive our patients to seek treatment. Or, perhaps, as Albert Einstein said, "Even our destiny is determined by the endocrine glands," and men are just becoming aware of this.

Whatever the exact mechanism of the increase in desire for testosterone replacement therapy in men, knowing the risks and benefits of testosterone and its alternatives are vital skills for today's practicing urologist. This article will focus on alternatives to testosterone therapy.

Why alternatives to T?

Male infertility specialists frequently manipulate the hypothalamic-pituitary-gonadal (HPG) axis in order to treat primary endocrine derangements or counteract the deleterious impact of exogenous testosterone on spermatogenesis (*Urol Clin North Am* 2014; 41:39-53). In order to appropriately manage hypoandrogenism, it is necessary to understand the HPG axis and the risks and benefits of the off-label use of female fertility agents in men (figure 1).

SECTION EDITOR

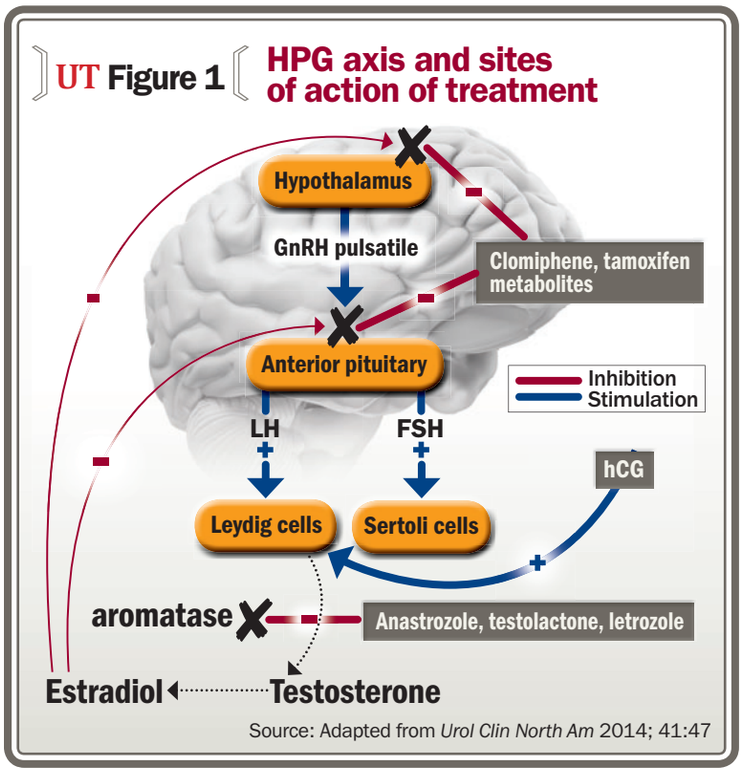
Steven A. Kaplan, MD, is E. Darracott Vaughan Jr. Professor of Urology at Weill Cornell Medical College and director of the Iris Cantor Men's Health Center, New York Presbyterian Hospital, New York. Follow him on Twitter at @MaleHealthDoc.

Dr. Hotaling **Dr. Brant**

Dr. Hotaling and **Dr. Brant** are assistant professors of surgery in the division of urology at the University of Utah, Salt Lake City.

An understanding of the impact of age and relationship of total, free, and bioavailable testosterone as well as estradiol and sex hormone binding globulin (SHBG) is also necessary (figure 2). Male aging is associated with a decrease in total testosterone and an increase in SHBG with a net effect of decreasing the bioavailable and free testosterone (*J Clin Endocrinol Metab* 2002; 87:589-98; *J Clin Endocrinol Metab* 2008; 93:2737-45). Given the well-known variability in free testosterone levels based on the assay used, we have used bioavailable testosterone as a screening tool for equivocal testosterone values and have typically followed PSA, HCT, and T (figure 3). For patients who are not obtaining lab tests within our men's health center, we will calculate the bioavailable testosterone based on testosterone, SHBG, and albumin (*J Clin Endocrinol Metab* 1999; 84:3666-72).

The most common reason that patients desire alternatives to testosterone therapy is fertility preservation. Many patients, and up to 25% of urologists based on a survey at AUA 2014, incorrectly believe that fertility will be improved through use of exogenous testosterone. Other common reasons are testicular hypotrophy, intolerance of the variability in testosterone levels associated with injection therapy, polycythemia, and mood instability. Typically, we monitor testosterone therapy with a PSA, hematocrit, and total testosterone at 3 and 6 months and then annually. Prior to initiating alternatives to testosterone therapy, we check levels of total testosterone, bioavailable testosterone, and estradiol.



Clomiphene

For patients desiring alternatives to testosterone therapy, our first-line medication is clomiphene citrate (Clomid), assuming the testosterone:estradiol ratio is greater than 10:1 and the patient does not have an estradiol >60 pg/mL. This medication works by blocking estrogen receptors at the level of the hypothalamus, is considered a selective estrogen receptor modulator, and is FDA approved for the treatment of ovulation induction in women. Clomiphene is well studied as a male infertility drug for

In mCRPC therapy...

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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.

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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

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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

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janssen

men with hypoandrogenism, and studies have shown that it is safe and well tolerated (*BJU Int* 2012; 110:573-8; *Urol J* 2010; 7:188-93).

We begin with clomiphene, 50 mg every other day (so patients do not have to split the pill in half), and repeat an endocrine analysis consisting of testosterone, SHBG, albumin (to calculate the bioavailable testosterone), and estradiol. If the estradiol is >60 pg/mL and bioavailable testosterone is >200 ng/dL with good symptomatic relief, we will decrease the clomiphene dose to 25 mg every other day. If the estradiol is >60 pg/mL and bioavailable testosterone is <200 ng/dL, we will switch the patient to an aromatase inhibitor with a goal of a testosterone:estradiol ratio of 10-20:1 (see below). Clomiphene is titrated up to 100 mg daily, repeating labs 2 weeks after each dosing change as necessary to achieve both symptomatic relief and bioavailable testosterone at least above 200 ng/dL.

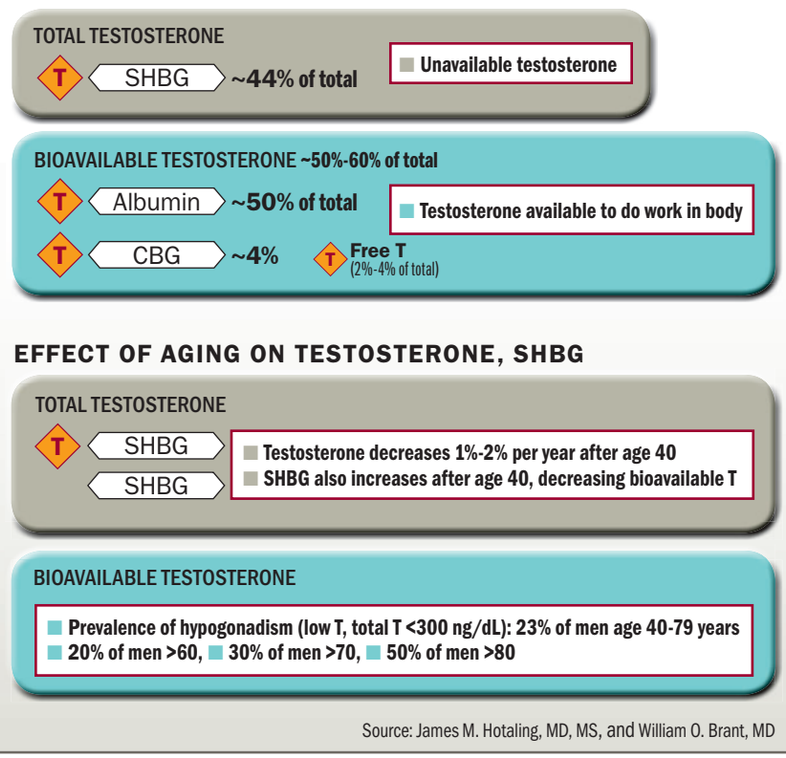
Once the patient is on a stable dose of clomiphene, we repeat a hematocrit, testosterone, and PSA every 3 months for a year and then annually for the duration of clomiphene therapy. Clomiphene is generally well tolerated, but some patients do not respond or have a paradoxical response (~6%), hence the need for rechecking labs 2 weeks after each change in dosing. Although there are no clear data on the subject, we have found that clomiphene provides only 75% to 80% of the symptomatic relief that men get with testosterone therapy.

Aromatase inhibitors

Should a patient have a testosterone:estradiol ratio less than 10:1 or hyperestrogenemia (estradiol >60 pg/mL), we typically initiate therapy with an aromatase inhibitor. Aromatase inhibitors work by blocking aromatase, which converts testosterone to estradiol, thus decreasing estradiol levels and reducing negative feedback. We use anastrazole (Arimidex), which we have found to be safe and effective, although some centers use letrozole (Femara).

Anastrazole, 1 mg daily, is prescribed, and we follow the same protocol as described for clomiphene but obtain a bone scan after 1 year of therapy due to the risk of osteopenia associated with decreased estradiol levels. Further, unlike clomiphene, where we commonly maintain therapy for patients for years, we attempt to keep the duration of anastrazole therapy less than 1 year due to the risk of osteopenia.

UT Figure 2 Impact of age on testosterone



Source: James M. Hotaling, MD, MS, and William O. Brant, MD

Human chorionic gonadotropin

If we are unable to make a man euandrogenic with clomiphene or an aromatase inhibitor, we move on to human chorionic gonadotropin or hCG. The reason this is a third-line drug for us is its high cost: $200-$400 per month versus clomiphene and aromatase inhibitors, which cost tenfold less.

We typically begin with 1,500 IU of hCG SC twice a week. hCG works on the Leydig cells to stimulate testosterone production. hCG is generally well tolerated and efficacious. While some have advocated using hCG in conjunction with testosterone to preserve testicular size, we have not employed this approach. However, we will use hCG in conjunction with anastrazole if men develop hyperestrogenemia while on hCG.

UT Figure 3

Checking for hypogonadism, treatment response

DIAGNOSIS

- Individualized assessment of symptoms drives treatment
- Blood draw before 10:30 AM
- Often need >1 draw as 10% variability between tests on same individual
- Check total testosterone and bioavailable testosterone

MONITORING TREATMENT

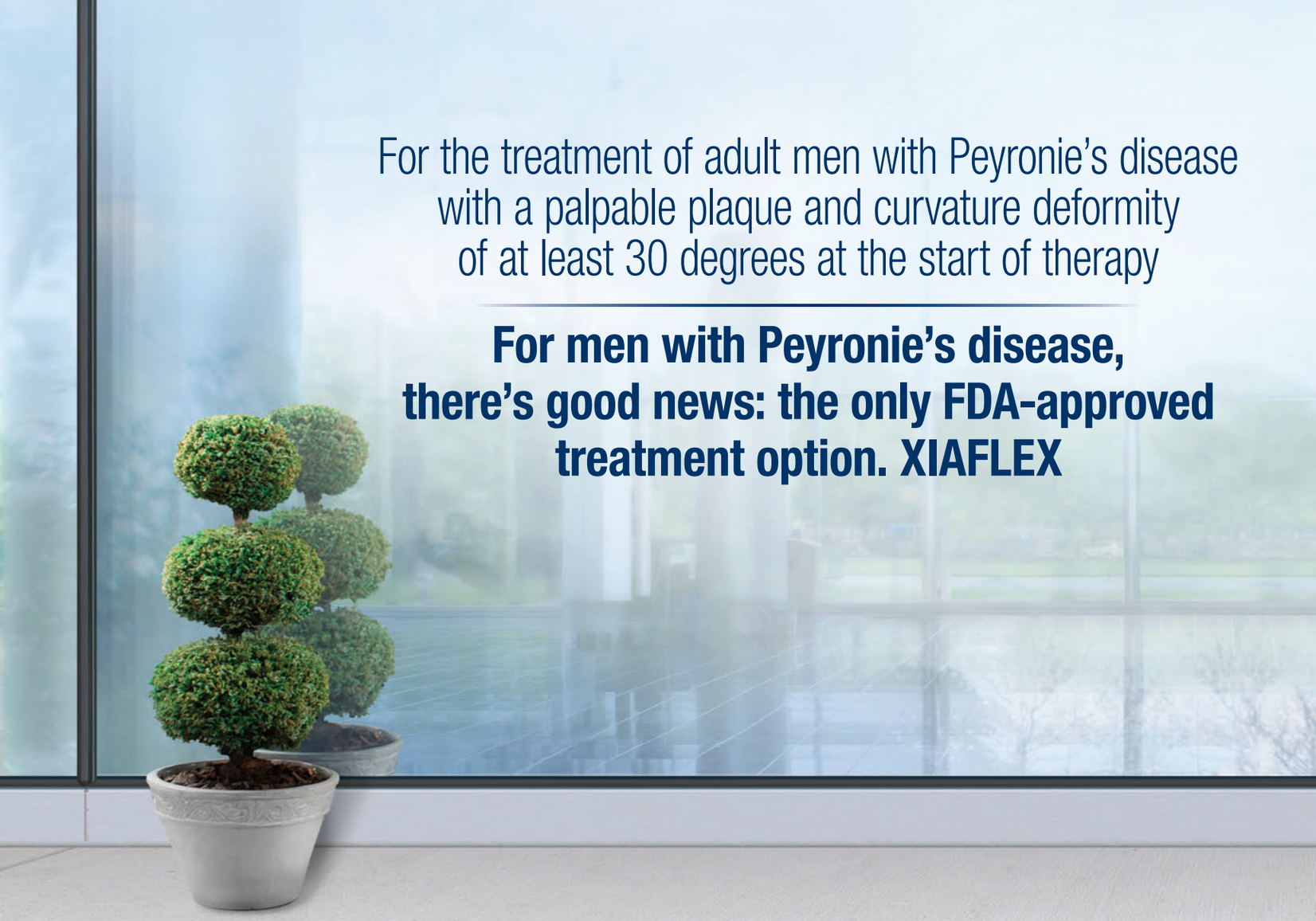
- Obtain PSA, hemoglobin, total T3 6 months after starting therapy and then annually thereafter
- Goal is to improve symptoms and keep testosterone in a safe range

Source: James M. Hotaling, MD, MS, and William O. Brant, MD

Conclusions

We counsel our patients that they should never take exogenous testosterone if they are planning on having children in the future. We have found that transitioning men from testosterone therapy to fertility-preserving medications such as clomiphene, anastrazole, or hCG is an iterative process that requires personalized treatments and multiple clinic visits. However, with this approach, we are able to transition nearly all men from testosterone to alternative therapy, although patients will rarely achieve the same degree of symptomatic relief.

Typically, it takes 3 to 9 months for spermatogenesis to return after transitioning men off testosterone and on to alternative forms of therapy. However, if men have taken anabolic steroids and have testosterone levels above 1,500 ng/dL, we counsel them that they may not ever see a full recovery of their androgenic axis. We do not routinely prescribe any over-the-counter supplements to men transitioning off testosterone therapy. UT



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.

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AUXILIUM
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EUGENE Y. RHEE, MD, MBA

Dr. Rhee was interviewed by *Urology Times* Editorial Consultant Philip M. Hanno, MD, MPH, professor of urology at the University of Pennsylvania, Philadelphia.

Q&A

WORKPLACE SAFETY

Violence against urologists: Data, communication needed

In the last 11 years, four urologists have been shot by patients, two fatally. A fifth urologist was shot in 1994 and a Colorado urology clinic was the site of violence in 2012, when a gunman held three people hostage before being shot by police. In this interview, Eugene Y. Rhee, MD, MBA, discusses several of these incidents, the challenges of collecting and sharing data on potentially dangerous patients, and what some institutions are doing to protect their practices. Dr. Rhee is chief of urologic surgery at Kaiser Permanente San Diego.

Q: ***A 2010 report from the U.S. Bureau of Labor Statistics showed that nearly 60% of assaults between 2003 and 2007 occurred in the health care and social assistance setting, and nearly three-fourths of those assaults were perpetrated by patients or health facility residents. When we think of potentially dangerous patients, we tend to jump to the field of psychiatry. What makes the field of urology particularly at risk for the dangerous patient?***

A: That's a good question. There isn't a good reporting mechanism that shows the true incidence of this problem. There have been a disturbing number of gun violence incidents committed against urologists. However, in looking at statistics from the Occupational Safety and Health Administration and the Bureau of Labor Statistics, there's no specialty-specific data on violent incidents.

There has been a lot of discussion as to why these acts have occurred. In the four recent cases in which urologists have been shot, the commonalities shared are that the perpetrators were male patients over the age of 60 years who had a pelvis-related issue that led them to violence. They were dealing with quality of life issues: pain, incontinence, or erectile dysfunction. These men had adjustment challenges that led them to ultimately violent acts.

Q: ***Let's discuss several of the high-profile examples of urologists who have been victims of violence. I know you're familiar with Drs. Reynaldo Hernandez, Ronald Gilbert, and Charles Gholdoian. Can you comment on these cases?***

A: These particular individuals have sacrificed immensely, and some of them are not with us today. One of my good friends is a SEAL team executive officer and I asked him how many members of his executive team have been lost or injured in the line of fire, and he said one over the last 10 years. I asked him, "What if I told you four urologists I know have been shot?" He replied, "You should really look at the scope of this."

Rey Hernandez was shot by a prostate cancer patient and survived. The gentleman had thought this out and planned it. It was a premeditated act.

Ron Gilbert didn't even know the patient who killed him. The shooter suspected that Ron had operated on him as a resident, which, it turns out, may not have been the case.

In the incident involving the fatal shooting of Garo Gholdoian, another urologist, Dr. Christine Lajeunesse, was also shot and injured, as was a patient in the hallway of the clinic. The shooter in that case passed through the waiting room with a warning that patients should leave, and marched into the practice's clinical area and started shooting. As in the other incidents, this was a premeditated event. It was not a spontaneous response to something.

In discussing these cases, the point is not to sensationalize; it is to understand that we all have an obligation to create a safe environment. We are all leaders in our own practices, we all have employees, and we also have our own personal safety to worry about. Personal safety is a very personal decision. Everybody has their own mindset about what they should do to secure their office. I urge everyone to think very diligently about this, because steps

Please see **VIOLENCE,** page 24

How can we be proactive in preventing patients from reacting badly to side effects from urologic procedures?
PHILIP M. HANNO, MD, MPH

We must manage patient expectations. We must discuss hard outcomes and how these patients could adjust to these outcomes. Identifying high-risk patients is critical to mitigate violent responses.
EUGENE Y. RHEE, MD, MBA

Survey: California urologists concerned about safety

63% had a patient who made them or their staff fearful for their personal safety

89% support a reporting system for high-risk patients, if legal

34% are taking measures to create a safe workplace environment, 38% are thinking about it, and 28% are taking no such measures

Source: California Urological Association 2013 survey of members

VIOLENCE

continued from page 23

can be taken to improve personal safety with not as many resources as you think you need.

Q: ***Urologic surgery can have numerous expected and unexpected side effects and complications, including the obvious ones of erectile dysfunction and incontinence. How can we be proactive in preventing patients from reacting badly to these conditions?***

A: We must manage patient expectations. We must discuss hard outcomes and how these patients could adjust to these outcomes. Identifying high-risk patients is critical to mitigate violent responses. There are ways to do this, such as observing body language and interacting with them (*West J Emerg Med* 2012; 13:17-25).

The challenge comes from the health care environment of today and our limited time in patient encounters. When I was a kid, I used to go to the hardware store. I learned how to build a birdhouse from the man who owned the store. Today, if you want to build a birdhouse, you go to a large warehouse type of store. You really have nobody to help you; you are in charge of understanding how to build your birdhouse.

In medicine, we are heading in the same direction, where patients don't really feel a kinsmanship with the physician. Part of this comes from patients switching insurance and thus physicians. Also, we're struggling to explain to patients about having prostate cancer and what it's like to have the prostate removed. Shortened visits can blunt your ability to bond with patients.

We have to ask ourselves: Is this really an appropriate patient for a given treatment? Is this patient educated enough to deal with the possible side effects? You can't argue about the side effects. They will happen; the complications of radical prostatectomy are well known in the literature, but you can make sure that the patient has adequate understanding before they give consent to proceed with treatment.

Please discuss the California Urological Association survey about workplace safety that was conducted last spring.
PHILIP M. HANNO, MD, MPH

The survey showed that 63% of doctors had a patient or knew a patient in their practice that made them fearful for their personal safety during the patient encounter.
EUGENE Y. RHEE, MD, MBA

Q: ***Please discuss the California Urological Association survey about workplace safety that was conducted last spring.***

A: A couple of weeks after Ron Gilbert was killed, the California Urological Association (CUA) emailed a three-question survey to our members. The survey showed that 63% of doctors had a patient or knew a patient in their practice that made them fearful for their personal safety during the patient encounter.

We also asked whether respondents would support a reporting system for high-risk patients, if it were legal. The response was overwhelming; 89% of doctors said yes.

The third question was: Are you taking any measures in your practice to create a safe workplace environment? One-third said yes, one-third said they are thinking about it, and one-third said no. To those who said no or that they were thinking about it, I urge them to consider the issues of safety in the workplace and understand liability risk.

Q: ***When is it reasonable to refuse treatment for a patient or discourage treatment because of fear he may not be able to cope with a bad result? When you get bad vibes about a patient, what do you do?***

A: This is a problem that happens every day for every health care provider, regardless if they are a urologist, nurse practitioner, or nurse. At some point, you have to determine whether or not a patient is too high a risk, and if you should stop seeing the patient. One must be careful how this is handled legally and there are privacy laws that must be taken into consideration.

It's not legal to create a list right now of "disruptive patients." This is where health policy advocacy can influence state legislation if it makes common sense.

When you talk to people who have survived these events, the common thread is that something was really "off" with the patient that the doctor had never felt before. I don't mean an argument; I mean something happened that made the doctor think, "something is really off about this patient, and now I am worried about my personal safety." As doctors, we take an oath that says we'll treat anybody, and not seeing a patient goes against that. I think that's why this issue is such a challenge in health care today.

Q: ***Do you know of any urologist who routinely carries a firearm?***

A: I gave a talk at the 2014 AUA Practice Management Conference on workplace safety, and it was very clear based on audience questions that there are urologists who carry a gun for personal protection. Every state is different in terms of what you're allowed to carry and what you're not. It's very complicated because even though you may be able to carry a concealed weapon under federal law, you may be in a state or employer group that has laws or policies strictly prohibiting guns in hospitals and/or other public places.

I must add that this is not a conversation about gun control; this is about what we are going to do as an organized urology community to enhance safety for all of us as best we can.

When is it reasonable to refuse treatment for a patient or discourage treatment because of fear that they may not be able to cope with a bad result?
PHILIP M. HANNO, MD, MPH

This is a problem that happens every day for every health care provider regardless if they are a urologist, nurse practitioner, or nurse. At some point, you have to determine whether or not a patient is too high a risk.
EUGENE Y. RHEE, MD, MBA

Q: ***There is a high incidence of posttraumatic stress disorder now among some patients at VA hospitals and other institutions. Can you describe***

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Watch excerpts from this interview, including discussion of attacks on urologists and recent survey data.

what kind of a threat management system the VA is using and how that could be applied in other places?

A: The VA has a very robust threat management system in place just for these situations, and it has led to other large institutions implementing similar systems. It's essential that grassroots urologists learn from these big systems in terms of what works.

The VA's system is very similar to what we have at Kaiser Permanente. We have a very structured threat management plan that has escalation parameters. There are protocols in place for how to respond to those alerts. Kaiser Permanente and the VA are proactive in making sure that there is continual education for all employees and providers.

Beyond this, some urologists are now taking personal security classes. Urology practices are seeking out security consultants. At the 2014 AUA Western Section meeting in Maui, HI, the CUA sponsored a threat awareness course. The CUA survey identifies this as an unmet need.

Q: ***I worked at a hospital where after a murder in the lobby, metal detectors were placed in the hospital entrance. The University of Pennsylvania has a patient screening apparatus in the ER. Do you think weapon screening should be standard coming into a hospital?***

A: As I mentioned earlier, security is very personal. A comprehensive security system can be very difficult to implement. It takes a lot of personnel, resources, and training. There are legal issues to consider. Implementing an expensive system that has cameras, metal detectors, and armed guards is not a sustainable plan, and it's not feasible in a typical urology practice.

A lot of studies have shown that metal detectors don't work. Earlier this year, at Olive View-UCLA Medical Center, a mentally disturbed patient with a knife ran through the metal detector, got into an elevator, and stabbed a nurse multiple times in the elevator. Did the metal detector prevent this incident from happening? The point is that a transparent look at operations within practices is vital before impulsively assuming certain safeguards need to be implemented.

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Q: ***Who is collecting data on these incidents?***

A: This is where the state societies and groups like the AACU and AUA can work together. We discussed this issue at the AUA Health Policy Council meeting. Additionally, the AUA's Office of Practice Management is starting to look at this closely. I really don't think the federal government is going to be able to give us pertinent specialty-specific data. We are going to have to gather data ourselves from within our urologic community; however, we are looking to have state urology societies work with state-level OSHA and government to help us with collecting the data. We are seeing an interest in doing this.

Q: ***You intimated that HIPAA prevents doctors from warning other doctors about potentially violent patients. I would guess that addressing this should be another high priority.***

A: There have been plenty of incidents in urology to justify considering bills that may help providers in the health care workplace that make sense on the state and perhaps federal level. In general, data show health care violence is becoming a big problem. The interesting thing about health care reform is that it's causing a lot of angst between the provider and the patient, and because of that, whether it's because we're running late or because insurance keeps dropping providers or patients, or there's a bill collection that needs to happen, there are challenging factors that influence our encounters with patients. That's very important to understand in terms of mitigating the risk of these encounters.

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

A: What is interesting is that it is legal for a urologist in the state of California to call another urologist and document that a patient is noncompliant to the physician's care. Documenting a patient as noncompliant to your care and that you had some difficult encounters is essential, but a phone call to another provider to discuss this noncompliance may be quite helpful on many different fronts. UT

Violence in the workplace: A physician assistant's perspective

Kevin Wayne, PA-C, *Urology Times* blogger

Despite living in the same town, practicing in the same specialty, and worshipping in the same faith, I didn't know of Dr. Ron Gilbert until the day he was killed. A urologist in my community, he was shot to death in an exam room on Jan. 28, 2013, by a patient he may have never even provided care for. The alleged gunman was apparently frustrated by the incontinence he suffered following a urologic procedure.

Then, less than a year later, Dr. Charles G. Gholdoian, a urologist in Reno, NV, was shot and killed at his practice. Dr. Gholdoian's partner, Dr. Christine Lajeunesse, was critically injured. It was reported that the gunman had been suffering with a possible complication from a prior vasectomy.

According to the U.S. Department of Labor's Bureau of Labor Statistics (BLS), there were 69 homicides in the health services from 1996 to 2000. In 2011, the BLS reported a total of 468 workplace homicides. Seven of these occurred among "health diagnosing and treating practitioners," four of whom were physicians.

I've cared for thousands of patients in the last 20 years, and while I have never been physically assaulted by a patient, I have occasionally felt threatened to the point where I've discontinued a visit and had a patient dismissed from my practice. These events, though uncommon, can be unnerving, given the unpredictability of human behavior. I know that I spent some time looking over my shoulder after a challenging patient encounter. I've had patients become belligerent after being denied refills on controlled substances. Another became threatening after his demands for a penile augmentation procedure were denied. And a recent threatening encounter involved a patient who told me that he would be "vengeful" if I suggested he be tested for HIV.

As health care providers, our prime directive is to help our patients. Unfortunately, this altruism does not exempt us from the possibility of a violent act by a patient against us or our staff. We have few defenses at our disposal should a patient decide to become violent during a clinic visit. It would behoove all of us to have a system in place to alert staff to a potentially escalating situation with a patient, and perhaps have the exam room laid out in a fashion that keeps the practitioner within easy reach of the door. Recruiting local law enforcement officials or representatives of federal or state occupational and health safety administrations may be of benefit in helping to develop a proper algorithm and exit strategy when faced with a potentially violent patient encounter.

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8.2 months longer
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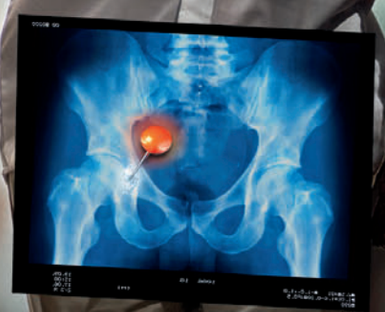

- RANK Ligand (RANKL) is produced by bone cells in the skeleton and is a key mediator of bone resorption[4]
- RANKL production is increased at sites of bone metastases, and stimulates osteoclasts to destroy bone[4]
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XGEVA® is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

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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.

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Oncology

Government alliances key to changing pay policies

Your participation, support needed to keep urology independent and viable

Coding and Reimbursement

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.

Payments for services in health care come by way of contracts, whether you are in private practice or an employee of a large specialty group, hospital, or other entity. Unfortunately, contracting is not easy, and contracts are influenced by many factors. In today's market, many feel that the only choice they have in negotiating a contract is not signing an agreement. While not signing a contract is often the right choice for the practice, opting out of everything is rarely a smart decision.

As health care payment policy is changing at a rapid pace, many have found that partnership with the government is the best way to affect overall payment policy. Reducing headaches from far-reaching policies has become too much for any one group, and working on state or national legislation has become an important tool for the practice of medicine.

The evolution of this process presents an interesting conundrum for many physicians. Government policies have created a morass of administrative guidelines that are a struggle to implement and result in receiving reduced payment from Medicare. The Affordable Care Act has influenced the marketplace dramatically, creating an environment that is just short of outright chaos. How can one possibly trust the government to assist in anything?

The history of governmental influence in the health care marketplace is long and convoluted. We will not attempt to provide an overview of this history; instead, we would like to recognize a few of those who, as volunteers, have been working on your behalf. There are too many to name them all, so we are going to mention those working on your behalf as groups. But bear in mind that the work of many is performed by a few and they all deserve our gratitude and support.

In our travels, we have heard many complaints about the representation that urology receives in the legislative process. We admit that no one is perfect, but more often than not, volunteer urologists and support staff from the AUA, urology offices, and friends of urology, like ourselves, fight to keep the practice of urology independent and viable as a business. Unfortunately, "we" do not always win and lately we have suffered a few setbacks. On the other hand, there have been some wins and there are opportunities for more.

The Medicare fee schedule and payment rules function as the backbone of the current payment system. In addition to being used by Medicare, Medicaid, TRICARE, and other federal entities, the Medicare payment system is used by nearly all private payers to update their systems in varying degrees and forms. The American Medical Association's Relative Value Scale Update Committee (RUC) makes recommendations to the government for appropriate relative values.

Urologists push RUC efforts

Urologists have been part of this process from the beginning and have done an unbelievably good job of keeping our relative values high compared to our colleagues. Basically, the committee works by recommending the work values for new services based on physician survey data. They are also now charged with defending the relative values that were previously set but are now considered misvalued by the Centers for Medicare & Medicaid Services.

The values recommended by urology representatives must be defended within the AMA RUC. Final recommendations of the RUC are then sent to Medicare, which has the option of accepting the recommendations or modifying them. In addition to data from surveys, this process requires strategy and coordination.

Understand that we are in a period in which the system is trying to reallocate funds from surgical specialties to primary care. This push usually translates to decreases in value for codes that are resurveyed, most not by choice at this time. It also means that new codes and new values are opportunities to revalue similar codes to lower rates. You can help by responding to requests to participate in physician work surveys.

New CPT codes and the retirement of unused codes or rewording of descriptors of different codes are the purview of the CPT Editorial Panel. Again, the AUA has representatives and staff dedicated to the support of the CPT coding system. The process is long and carefully approached by the AUA and AMA. Striking a balance between correct and complete coding and the maintenance of values that will eventually have to be assigned to these codes by the RUC is difficult and highly regulated by the AMA process. The process for a new CPT code for new technologies is long and tedious, and it's important to

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

understand that the system is in some ways its own worst enemy. New codes have to represent widely used services or procedures in order to be considered, been granted FDA approval, and be supported by peer-reviewed literature. A balance between utilization and the painful process of obtaining reimbursement for services without a CPT code is considered prior to accepting a new code and the impact each entails.

The AUA Coding and Reimbursement Committee (CRC) is involved in both the CPT and RUC, as well as policy decisions that are brought by third-party insurers including Medicare. The work by the CRC impacts every urologist and requires significant time and effort from the staff and volunteers.

You may be asking yourself, "Why do I need to know about these efforts? I am just a hard-working practicing urologist." The reason is simple. If you see inequities in the system and/or rules that prevent you from being paid appropriately for services, the best way to bring about change is to write a letter to the CRC. Detail the problem and your suggested solution. The CRC and the AUA or AMA cannot always solve these issues, but the best way to effect change is through the consolidated approach of the specialty voice.

States finding solutions

The states are becoming increasingly important as a melting pot for new ideas and new ways for delivering health care, paying physicians, solving systems problems, etc. One good example in which we are directly involved is Colorado's Clean Claim Task Force, which is an effort to simplify the claims processing system by implementing a single claims edit for all private payers. What a novel idea! Again, urology is represented well in the process, focusing on correct coding from a clinically based approach. The AUA was one of the first specialty organizations to join this effort 2 years ago.

We are in a period in which the system is trying to reallocate funds from surgical specialties to primary care.

Other states are looking at adopting a similar approach, and we could use more. Like the concept of prompt pay and all-payer claims datasets, the more states that adopt legislation to follow the ideals of the single edit sets, the more likely the solution becomes a reality.

Other state groups have also pursued the goal of simplifying health care administration through state legislatures. One example is Ohio (through the Ohio Urologic Society and its State Government Affairs Monitoring Committee), which has been active in bringing revision to PSA testing guidelines and prior authorization. Ohio physicians are also bringing attention to tort reform needs, physician unions, problems with Medicaid expansion, and compounding pharmaceuticals. Specifically, they have developed an excellent working relationship with the Carrier Advisory Committee in Ohio and in dealing with the Medicare Administrative Contractors medical director.

Other model state urologic societies and collaborative efforts among urologists and state medical societies such as those in Florida, Washington, and California have made significant inroads with legislators to block efforts to remove ancillary ownership, revise men's health initiatives, and decrease administrative roadblocks.

Additionally, the AUA and state groups have been supplemented in their efforts by the American Association of Clinical Urologists, the Large Urology Group Practice Association, and other subspecialty groups at the state and national level.

Although we have avoided mentioning the names of the individuals who drive many of these efforts, again it is often the work of a few motivated urologists and the staff of the organizations that do the majority of work. We see a strong need for more to be involved. Support can be provided in many ways. Financial contributions to political campaigns, political action committees, societies, and special interest groups are more critical than ever. Donating time is also key. Consider getting involved locally or nationally with your societies and the AUA Practice Management and Public Policy committees.

The chaos of today's health care marketplace evolution requires a unified voice in supporting the practice of urology. It also requires that you build alliances with individuals, groups, and ideas that you may not agree with 100%. Remember as well that the focus for these issues remains similar to those that you have in your daily practice. Correct coding, administrative cost reduction, and clinical relevance of services are all a part of the campaign for urology to maintain patient access to quality care. UT

State society conference: Vigilance in the political process essential

Daniel R. Shaffer, AACU Executive Office

Leaders of state, national, and subspecialty urologic societies converged in Rosemont, IL in September for a weekend of health policy discussions and advocacy tips with public officials, policy experts, and fellow urologists. One of the themes reinforced at the 7th Annual State Society Network Advocacy Conference, hosted by the AACU, was the importance and impact of physician engagement in the political process.

That message was apparent from the opening dinner, when Connecticut State Representative Prasad Srinivasan, MD (R-31 Glastonbury), described his journey from medicine to politics and his experiences in the Connecticut General Assembly as its only physician representative. Instrumental in defeating a 2012 bill aimed at weakening the state's certificate of merit law, one of the reforms to Connecticut's medical liability laws enacted over the years, Dr. Srinivasan also shared his insights into ways physicians can become better engaged in the political process.

Mark Stovksy, MD, who ascended to the AACU presidency during the conference, led a panel discussion on in-district federal advocacy, where panelists Mark Edney, MD, the AACU's newly elected secretary-treasurer, and Christopher Gonzalez, MD, AUA Health Policy vice chair, illustrated the importance of building and maintaining relationships with federal representatives in-district and offered suggestions on how.

A dramatic example of what can be achieved with strong physician engagement and a coordinated advocacy effort among urology and other specialties was demonstrated when California urologists Eugene Rhee, MD, and Aaron Spitz, MD, were joined by California Urological Association President David Benjamin, MD, and California Medical Association Associate Director for Government Relations Stuart Thompson, JD, for a presentation on the defeat of California Senate Bill 1215. All of the panelists were involved in this effort on the ground and were able to offer a detailed eyewitness account of the bill's defeat. Had this bill become law, the in-office ancillary services exception to California's physician referral law would have been essentially eliminated throughout the entire state, dramatically affecting the delivery of health care and patient access to independent, integrated medical services.

Attendees were presented with a lot of information and suggestions to take back to their respective states and societies. However, of the topics stressed at this year's conference, none was more important than the necessity of physician vigilance in the political process.

For more about this meeting, please see *bitly.com/statesociety*.

The first World Congress of Endourology & SWL (WCE) in 1983 solidified endourology's place in medicine. That same year, we formalized nearly a decade of experience in the field and attended WCE as Cook Urological.

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Prostate Ca surveillance: Overcoming obstacles

Identifying/tracking patients, lack of consensus on candidacy among hurdles; here are steps to take

It has been more than 2 years since the U.S. Preventive Services Task Force released its final grade "D" recommendation concerning PSA-based screening for prostate cancer, and the impact of the recommendation on urologists, patients, and prostate cancer incidence, morbidity, and mortality is still being evaluated (*JAMA Intern Med* [online] Sept. 1, 2014).

The recommendation against PSA-based screening, the basic research it drew upon, and the potential for overtreatment of low-risk disease have all served to heighten awareness about the side effects of definitive treatment for prostate cancer and the option of active surveillance.

In a series of articles, I will examine the challenges and the impact of conducting active surveillance in the context of the business of medicine—how a significant shift in approaching and treating patients with prostate cancer might be expected to affect health care operations, reimbursement, or income for the practicing urologist. In this first installment, I will review the challenges of implementing active surveillance in a practice as well as ways to surmount these obstacles.

Identifying, tracking patients on surveillance

Assessing the impact of a shifting role for active surveillance in the busy urology practice comes with some challenges. First, there is no easy way to identify how many and which patients in a practice—or in national benchmarks—are "on" active surveillance. No distinct procedural (CPT) or diagnostic (ICD-9 or ICD-10) code systems in common use today incorporate this concept, so these patients cannot be easily identified in billing or clinical data sets. One clinical terminology system—SNOMED CT (Systematized Nomenclature of Medicine-Clinical Terms)—does contain concepts that could be combined to create a meaning of "active surveillance for prostate cancer," but the terminology is not in widespread use among urologists or their electronic system vendors today.

No consensus exists today on what services constitute "active surveillance."

To face this and other challenges with the many options available to patients with prostate cancer, many urology and oncology practices have employed "patient navigators." In some cases, the navigators also track patients (manually) on their journey and can report basic metrics on relative frequency of treatments for prostate cancer. For most, though, even establishing a baseline number of patients on active surveillance is a challenge.

A second challenge is a lack of established consensus on candidacy for active surveillance. According to research from the United Kingdom and United States, it can take 10 to 20 years for findings of research to be incorporated into common clinical practice (*http://bit.ly/10wL5SQ*). The work on identifying ideal candidates is arguably less than 10 years old and is rapidly evolving with the introduction of new genetic and molecular testing. The critical role of pathologists in helping determine candidacy for alternate management approaches has only recently been recognized and exposed another area ripe for consensus making (*Arch Pathol Lab Med* 2014; 138:1387-405). Perhaps the most relevant clinical guideline endorsed by AHRQ on the role of active surveillance in localized prostate cancer, published in late 2011, simply calls for more research—including on which men are appropriate candidates for surveillance (*http://1.usa.gov/1ta7ShO*).

A related challenge is that even if a firm consensus existed on candidacy for this management approach—for example, based in part on pathologic characteristics of the biopsy specimen—many clinical systems are not configured to receive, store, or interpret this information in a consistent and computable manner. Many lab interfaces are proficient at passing discrete data like PSA values and not so proficient at digitizing big documents like histology reports. Interfaces can be constructed to onboard information such as Gleason grade, Gleason score, percent core involvement, and number of positive cores, but in this author's experience they are not in widespread use today.

To speed the adoption of new management approaches—like active surveillance—based on clinical characteristics of the patient, urologists need clinical decision support (CDS) tools that can gather the information and "assist" clinicians with their tasks. These tools exist, but without the data in a computable format, they remain largely unused. The promise of a popup window that says "Hi, based on this patient's recent new diagnosis of prostate cancer and assignment of risk based on their PSA, T stage, age, comorbidities, and biopsy characteristics, he *may* be a candidate for active surveillance" is mostly unrealized today.

A final challenge is that no consensus exists today on what services constitute "active surveillance." Unanswered questions include: "Does every patient need to have a follow-up biopsy?"; "How and how often should patients be monitored?"; "What are the thresholds that trigger a recommendation to move from active surveillance to traditional treatment?"; and "What is the role of genetic and molecular testing in monitoring patients on active surveillance?"

Centers that have advanced the science in this area have well-established protocols, but community urologists who have begun to embrace active surveillance have not necessarily adopted a standard approach for the reasons mentioned above (delay in translating science to practice). Finally, it will be years before

Practice Pointers

- There is currently no easy way to identify how many and which patients in a practice—or in national benchmarks—are "on" active surveillance.
- Another challenge of active surveillance is the lack of established consensus on candidacy for it.
- To speed the adoption of new management approaches—like active surveillance—based on clinical characteristics of the patient, urologists need clinical decision support tools that can gather the information and "assist" clinicians with their tasks.
- Practices should be thoughtful about creating ways to identify and track their patients who are newly diagnosed with prostate cancer.

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.

outcomes will be known that could inform the answers to these questions.

Steps to take

How should these challenges be addressed today, and what impact do they have on the office practice?

First, practices should be thoughtful about creating ways to identify and track their patients who are newly diagnosed with prostate cancer. Options include maintaining a list of patients in spreadsheet form (many EHRs allow the creation of a "patient list," but a simple Excel spreadsheet will also suffice); creating a custom template in your documentation system that includes searchable keywords or metadata; assigning a custom ICD-9 or CPT code in your practice management system that signifies the patient is on active surveillance; or using the "problem list" functionality of your system to create a searchable custom problem—even better, attach a SNOMED CT concept or other clinical term to it. If your EHR doesn't use SNOMED, you can "borrow" another term you are likely to never use.

Until a national guideline dictates otherwise, create your own criteria for identifying candidates for active surveillance and follow those criteria.

Second, until a national guideline dictates otherwise, create your own criteria for identifying candidates and follow those criteria. Resist the temptation to only "copy forward" textual information you may have entered that could determine candidacy and is not computable. When the day arrives that information systems can process the information to help you, you will be prepared.

Encourage your vendor to be proactive about creating CDS tools in preparation for that day. If you already have CDS tools, create a rule and use it. If you haven't already done so, consider investing in a lab information system interface that stores histology reports in computable formats (ie, discrete data).

Finally, standardize your active surveillance protocol and share it with your staff. Help them understand this is a plan just like a radical prostatectomy, and teach them how to schedule the appropriate tests, follow-ups, and reminders the same way each time. Develop patient handouts, web pages, or other artifacts to support and institutionalize your standard approach. Create an order set in your EHR that is specific to active surveillance (and use it!).

If you modify your approach, update your staff, your materials, and your electronic order sets. This is a significant change in the practice, and it needs to be actively managed.

Bottom line: Active surveillance is a new management paradigm that closely resembles trends in primary care, including "population health management" and "disease management." All have in common an active approach to monitoring and managing according to evidence-based best practices. When usable and computable clinical guidelines on active surveillance have received national endorsement and are widely incorporated into clinical practice and CDS tools, today's challenges and uncertainty will perhaps fade. In the meantime, urologists should see active surveillance as an opportunity to standardize approaches in the practice and continue to think about managing populations as well as individual patients.

In a future article, I will examine the possible impact of active surveillance on reimbursement and income in the urology practice. UT

Which charitable trust strategy is best for you?

Splitting ownership interests an option for those unable to contribute entire asset

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 I'm interested in a more formal charitable gifting strategy to minimize taxes, but would also like to supplement my retirement income. What options are available?

A There are a number of reasons to give to charitable causes. From a purely financial standpoint, gifts to a charity during lifetime or at death will reduce the size of the gross estate, which may reduce or even eliminate the amount of estate taxes due at death. An additional benefit of lifetime gifts is that a current income tax deduction is available, within certain percentage limitations.

If the estate owner, based on his current financial situation, is not willing or able to contribute an entire financial asset during his lifetime, a split-interest, deferred gift is something to consider. The ownership interests in an asset can be split or divided into two parts: a stream of income payable for one or more lifetimes or a term of years (the income interest) and the principal remaining after the income term (the remainder interest). When the estate owner retains the right to the income but transfers his or her rights in the remainder to a trust, it is called a charitable remainder trust.

To qualify for an income tax deduction, the trust must be a unitrust, an annuity trust, a pooled income fund, or a charitable gift annuity.

Charitable remainder unitrust. In this type of trust, the donor retains the right to a fixed percentage of the fair market value of the trust assets, with the trust assets being revalued annually. If the value of the assets increases, so does the annual payout, and vice versa.

Charitable remainder annuity trust. This trust is similar to the unitrust but instead pays a fixed dollar amount each year.

Pooled income fund. Assets are transferred to a common investment fund maintained by the charity. Each donor receives annually a share of the income from the fund, in proportion to the contribution made. These annual payments continue for the lifetime of the donor and spouse. At death, the corpus of the donor's gift, together with any capital gains, passes to the charity. Payments will increase or decrease with the investment performance of the fund.

If you're an estate owner wishing to make a gift to charity but not willing to contribute an entire financial asset during your lifetime, consider a split-interest, deferred gift.

Charitable gift annuity. The donor transfers the asset directly to the charity, in exchange for the charity's agreement to pay a fixed lifetime annuity.

The amount of the income tax deduction is dependent upon the percentage of the income interest and the period over which it will be paid (usually the life of the donor and his or her spouse). This calculation is determined from the mortality tables published by the government.

On the other end of the charitable gifting spectrum are those individuals who want the charity to receive only the income and not the asset itself. A charitable income or lead trust is the reverse of the charitable remainder trust. The income interest is assigned to the charity, usually for a period of years, and then the remainder generally passes to the donor's heirs. The amount of the estate tax deduction and the amount left for the heirs will depend upon the number of years income is to be paid to the charity, the size of the annual payments, and the investment results achieved by the trustee.

There are many factors to consider prior to implementing any type of charitable trust strategy. To determine whether it makes sense for your particular situation, be sure to consult with your tax and estate-planning advisers.

Q With all the talk of rising interest rates, what should bond investors focus on to reduce their risk?

A Investors should always consider ways to manage risk in their fixed-income portfolios, especially with concerns of rising interest rates. Here are a few guiding principles:

Hold shorter term issues. This approach may help reduce volatility while enhancing liquidity. Also, fixed-income investors who hold investment-grade bonds must consider their exposure to changes in interest rates. Bond prices move in the opposite direction of interest rate changes—and the longer a bond's maturity, the greater its price change.

Stay broadly diversified. Holding many bond issues and avoiding concentration in a particular industry, sector, or issue type can help reduce the impact of a few non-performing bonds. If default rates rise, investors with a well-diversified bond portfolio should be less exposed.

Focus on quality and use market pricing to confirm credit ratings. The most creditworthy bonds are those rated AAA or AA, and most of the current problems involve lower rated bonds. Although ratings are useful, recent history in the mortgage-backed securities market has shown that a bond may not be rated accurately. A bond rated AAA should trade in a similar price range to other bonds with similar characteristics and a comparable rating. UT

Financial Tips

- In a charitable remainder trust, the estate owner retains the right to the income but transfers his or her rights in the remainder to a trust.
- To qualify for an income tax deduction, a charitable remainder trust must be a unitrust, annuity trust, pooled income fund, or charitable gift annuity.
- In managing risk for fixed-income portfolios, guiding principles include holding shorter term issues, staying broadly diversified, and focusing on quality and using market pricing to confirm credit ratings.

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.

Speak Out

How do you manage large kidney and ureteral stones?

"Distal stones we treat medically first, then with ureteroscopy. Proximal stones we usually treat with ESWL, sometimes percutaneous treatment, depending on the stone's location and size. If the stone is very large and in a location where ESWL is less likely to be successful, you think harder about doing the percutaneous approach. We generally only use ureteroscopy on distal stones.

We do a lot of ESWL. There's a tendency to do multiple ESWLs, even where the percutaneous procedure is equally appropriate and requires only one treatment. When you describe both procedures, patients decide ESWL sounds like a better way to go. ESWL is less traumatic and the results are good."

Geoffery Engel, MD
Elk Grove Village, IL

"For ureteral stones, my primary treatment approach is ureteroscopy.

Dr. Fuchs

We had the first lithotripter on the West Coast and patients expected the least invasive treatment, but we found that a good third of stones did not respond. Stones in the ureter for any prolonged period did not respond well to shock wave lithotripsy regardless of the amount of energy used.

Eventually, we decided that we would treat all stones in the ureter that couldn't be pushed up with a ureteroscope, breaking them up with direct-contact lithotripsy. Then, the holmium laser became available and worked so well that we eventually treated virtually all ureteral stones with the laser.

If patients don't have spontaneous stone passage, I discuss lithotripsy—and quote a success rate between 50% and 90%—and ureteroscopy, with basically 100% success.

For kidney stones larger than 3 cm or the branched stones, PCNL is clearly the treatment of choice, but with better metabolic evaluations and medical management, very big stones are not as common anymore."

Gerhard Fuchs, MD
Beverly Hills, CA

"It depends on how big the stone is. Bigger stones of course we do percutaneously. I discuss shock wave lithotripsy versus ureteroscopy with the patient for smaller stones. I tell them ureteroscopy probably has a higher chance of clearing the stones but shock wave is probably the safest.

If it were me, I would probably try shock wave before ureteroscopy. But some people say, 'I want one-and-done;' the answer to that is ureteroscopy.

Most people do try shock wave, but I'm very open about it and let them know that we probably have a higher chance of getting rid of the stones with the ureteroscopy.

My experience with shock wave lithotripsy is probably a little better than what textbooks and articles report. We probably only have to repeat ESWL or go to ureteroscopy about 20% of the time."

Marc David Benevides, MD
Cary, NC

PREPARE

continued from page 1

alter how urologists and other physicians do business.

"It's going to completely change the way we document our patients and patient encounters. It's really going to change medicine," Dr. Rubenstein said. "Not only do doctors need to understand the specificity of ICD-10 and how to code, they need to understand the codes and need to understand what to document—not only if they're choosing the codes but if someone else is helping choose the codes for them."

If they don't, reimbursement is in jeopardy, Dr. Rubenstein says.

Practice readiness is only one piece of this potentially disruptive event. It doesn't ensure a smooth transition. In fact, part of physicians' readiness has to include preparing for the system's failure—at least initially.

ICD-10: A primer

The ICD is owned by the World Health Organization (WHO). In the United States, it was decided several years ago that ICD would be

"Not only do doctors need to understand the specificity of ICD-10 and how to code, they need to understand the codes and need to understand what to document."

JONATHAN RUBENSTEIN, MD

the coding system that the nation's providers would use for billing purposes.

"The problem is, ICD-9 is really outdated. It was created in 1977. ICD-10 is a much larger system. It's much more detailed. It really uses much more modern language. But because it's new, we have to learn a new system. I think it's really unrelated to ICD-9, just the way that it is set up," Dr. Rubenstein said.

W. Jeff Terry, Sr., MD, a Mobile, AL urologist and state delegate who works on behalf of the American Medical Association on opposing ICD-10 implementation, says it is the AMA's policy to "vigorously work to stop the implementation of ICD-10 and to reduce its unnecessary and significant burdens on the practice of medicine."

According to the AMA, implementing ICD-10 alone requires physicians and their office

ICD-10 PREPARATION: A CHECKLIST FOR UROLOGISTS

Mark Painter, CEO of PRS Urology, and **Jonathan Rubenstein,** MD, a urologist in Baltimore and member of the AUA's Coding and Reimbursement Committee, recommend this checklist for ICD-10 urology practice transition. For a printable version of this list, visit *bitly.com/UT-ICD10-checklist*

- ☐ **Create a team.** If you haven't already done so, start in November or December 2014 to develop a transition team to look at four practice departments: information technology (IT), clinical, billing and coding, and administration and finance. Small practices might have one champion. Larger practices might have groups of people assigned to analyze readiness in each of these areas.
- ☐ **Revisit ICD-9.** As soon as possible, take a look at how you're coding with ICD-9. Anything you're doing wrong in ICD-9 will come back to haunt you in ICD-10.
- ☐ **Be sure systems are ready.** IT staff should make sure a practice's clearinghouses, electronic medical record, and practice management system are ready to go. If your EMR system is not ICD-10 ready and might not be by Oct. 1, 2015, change your system now.
- ☐ **Learn new documentation.** Providers need to learn ICD-10 documentation requirements and start processing and documenting as early as possible, as though they were in an ICD-10 environment. Prepopulate your EMR system with ICD-10 codes so you can be ready for Oct. 1, 2015.
- ☐ **Test, test, test.** IT staff should test whenever possible throughout the year. CMS is offering a test Nov. 17-21, 2014. As the deadline for ICD-10 gets closer, test more. Consider testing where clinical staff code for ICD-9 and ICD-10 simultaneously a couple of times each month in April, June, and July. Step up the testing pace to about once or twice a week in August and September.
- ☐ **Book onsite training now.** Come August or September, the practice might need that last training session with the EMR vendor. But if you try to book the session close to crunch time, the vendor might be overwhelmed. Make the appointment now and make sure it can be canceled.
- ☐ **Check payers' readiness.** IT or administrative staff should check with your payers for their readiness or timelines for readiness. The goal is to find out if they've tested for ICD-10 readiness. If they have not tested and plan to go live without a test, plan for that payer's reimbursement to be disrupted. You can do this as late as April 2015.
- ☐ **Have a backup.** Develop a paper tool (an old-fashioned paper superbill) as a backup, just in case there is a glitch in communication between your EHR and practice management system. Add some cheat sheets for how to communicate diagnoses for services provided in a hospital setting. Those tools need to be designed and tested between January and April 2015.
- ☐ **Plan for glitches and reimbursement woes.** Either have a 60- to 90-day cash reserve or credit line available in case of cash flow problems beginning Oct. 1.
- ☐ **Conduct training.** Start training clinical and billing staffs on ICD-10 between April and August. Get urology-specific training. Training through a hospital system, for example, is generic. The AUA offers a basic ICD-10 training course on *www.auanet.org*. PRS Urology has ICD-10 webinars and live seminars scheduled starting in April 2015; for more information, visit *http://prsnetwork.com/icd10training/*. (Also see, "ICD-10 resources online," page 44.)

staff to contend with 68,000 codes—a fivefold increase from the current 13,000 codes. Hospitals will have to contend with 87,000 codes. What does this mean to urologists? It depends who you ask. Painter says it might not mean much. Dr. Terry says it could be overwhelming.

"We've started pulling different numbers. If you look at the broad spectrum… of where urology codes are, we figure there is about a 20% increase in codes," Painter said. "But that's discounting the use of external cause codes. We have external cause codes in ICD-9 and don't use them, and nobody is expecting that ICD-10 is all of the sudden going to be requiring external cause codes."

Painter says the majority of urology revenue is driven by, at most, 50 different diagnosis codes in ICD-9. That should grow to about 70 in ICD-10.

"If you really look at the average urologist and what drives reimbursement, it's even smaller than that. That code set is down to 20. Everybody is trying to tackle the whole thing, when in reality what you need to do is find out where you are with ICD-9, then focus on the translational piece and dealing with those problems," Painter said.

Dr. Terry says it's a myth that urologists won't have a big change in their coding with ICD-10. In Alabama, he says, when a patient has a kidney stone, he has to code for more than just a kidney stone.

"The major insurance carrier in Alabama plans to require physicians to code for all the other problems the patient has, such as high blood pressure, diabetes, coronary artery disease. Diabetes has approximately 250 codes [in ICD-10]. How am I going to get the right one? If I have the wrong diabetes code, that could affect my pay. If I code it differently than the hospital, that could affect my pay. I barely know what diabetes is. I'm a urologist!" Dr. Terry said.

"Everybody is trying to tackle the whole thing, when in reality what you need to do is find out where you are with ICD-9, then focus on the translational piece and dealing with those problems." MARK PAINTER

Even in the best-case scenario, the ICD-10 transition is a huge undertaking for practices already burdened by government regulations and unfunded mandates.

"Physicians in our country are looking at huge increases in capital outlays to meet EMR requirements and, at the same time, are looking at penalties for not meeting the meaningful use requirements, for not meeting a threshold for e-prescribing, and for not reporting appropriately in the PQRS program, along with a 2% reduction in payment due to sequestration," Dr. Terry recently wrote in a personal communication.

"I agree we need to have an updated coding system, but we must do it the right way so as not to put physicians out of business and disrupt patient care." W. JEFF TERRY, SR., MD

And the cost to physician practices to make the change to ICD-10 is dramatically higher than previously estimated, according to a recent study initiated by the AMA and conducted by Nachimson Advisors.

The 2014 study found, in some cases, the estimated ICD-10 implementation costs are nearly three times what had been predicted in 2008 by Nachimson Advisors, according to an AMA press release. Why? The newer study includes higher amounts for testing and risk of payment disruption. For example, in 2008 the predicted cost to implement ICD-10 ranged from $83,290 for a small practice, $285,195 for a medium practice, and $2,728,780 for a large practice. The 2014 study suggests a small practice might spend $56,639 to $226,105; a medium practice, from $213,364 to $824,735; and a large practice, from $2,017,151 to $8,018,364, according to the AMA release.

Coding ICD-10 style

Dr. Rubenstein says urologists might experience some of the most notable changes in trauma codes because of their specificity.

"There are so many nuances to choosing the correct code," Dr. Rubenstein said. "In addition, for a lot of the trauma codes, the doctor needs to document in the chart… whether it's the first time they're seeing the patient for this condition, a subsequent time they're seeing the patient for the condition, or if they're seeing the patient for a sequela of the trauma."

In ICD-10, unlike ICD-9, urologists will in some cases need to specify laterality. They'll have to code for either right-side or left-side kidney cancer, according to Dr. Rubenstein.

"You have to document that and understand there's a unique code for each one of those conditions," he said.

Laterality isn't necessary, however, when coding for a kidney stone or epididymitis.

Regardless of how good an EMR system is or how astute professional billers are regarding ICD-10, urologists and other physicians are at the frontlines of coding. They have to

Please see **PREPARE,** on page 44

POSSIBLE FIXES

The main problem with ICD-10 in the U.S. is its flawed implementation and huge impact on every aspect of the health care system, according to W. Jeff Terry, Sr., MD. For physicians who have small practices and might still be struggling with EMRs and other government regulations, ICD-10 implementation could be the last straw, he says.

Solutions, according to Dr. Terry, include:

- **Uncouple the ICD diagnosis code from the CPT payment code, so physicians' payments wouldn't hinge on correct coding. This, he says, is the most important fix.**
- **Use ICD-9 and ICD-10 concurrently for the first year, until the glitches are worked out of the system.**
- **Adopt ICD-10 as scheduled, on Oct. 1, 2015, but have assurance from CMS that it will not penalize physicians for coding mistakes in the first year. The concern is whether other payers would honor the grace period.**
- **Bypass ICD-10 and transition to ICD-11, which is scheduled to come out in 2017 in its raw version. "We're going to spend all this money on ICD-10. Then, CMS is going to mandate that we use ICD-11 in 5 to 10 years," Dr. Terry said.**

Jumping to ICD-11 would be impossible, according to Jonathan Rubenstein, MD. "ICD-11 won't be ready for several years, and it takes several years to clinically modify the newest version of ICD for clinical use here in the U.S.," Dr. Rubenstein said. "And we need ICD-10 to be able to transition to ICD-11."

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Important Safety Information (continued)

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Intracavernous injections of CAVERJECT can lead to increased peripheral blood levels of prostaglandin E_1 (PGE_1) and its metabolites, which may lead to hypotension and/or dizziness.

Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.

The safety and efficacy of combinations of CAVERJECT and other vasoactive agents have not been systemically studied. Therefore, the use of such combinations is not recommended.

Careful instruction in proper patient handling and injection techniques may minimize the potential for needle breakage.

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INDICATION AND USAGE

CAVERJECT IMPULSE is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

Intracavernosal CAVERJECT is also indicated as an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CONTRAINDICATIONS

CAVERJECT should not be used in patients who have a known hypersensitivity to the drug, in patients who have conditions that might predispose them to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia, or in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease. Patients with penile implants should not be treated with CAVERJECT.

CAVERJECT is intended for use in adult men only.

CAVERJECT is not indicated for use in children or newborns.

CAVERJECT should not be used in men for whom sexual activity is inadvisable or contraindicated.

WARNINGS

Prolonged erection defined as erection lasting > 4 to ≤ 6 hours in duration occurred in 4% of 1,861 patients treated up to 18 months in studies of CAVERJECT Sterile Powder. The incidence of priapism (erections lasting > 6 hours in duration) was 0.4% with the same length of use. Pharmacologic intervention and/or aspiration of blood from the corpora cavernosum was performed in 2 of the 7 patients with priapism. To minimize the chances of prolonged erection or priapism, CAVERJECT should be titrated slowly to the lowest effective dose. The patient must be instructed to immediately report to his prescribing physician, or, if unavailable, to seek immediate medical assistance for any erection that persists longer than 4 hours. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

PRECAUTIONS

General Precautions

1. CAVERJECT IMPULSE is designed for one use only. Following a single use, the injection device and any remaining solution should be properly discarded.
2. The overall incidence of penile fibrosis, including Peyronie's disease, reported in clinical studies with CAVERJECT Sterile Powder was 3%. In one self-injection clinical study where duration of use was up to 18 months, the incidence of fibrosis was 7.8%.

   Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis. Treatment with CAVERJECT should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.
3. Intracavernous injections of CAVERJECT can lead to increased peripheral blood levels of PGE_1 and its metabolites, especially in those patients with significant corpora cavernosa venous leakage. Increased peripheral blood levels of PGE_1 and its metabolites may lead to hypotension and/or dizziness.
4. Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.
5. Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with CAVERJECT.
6. The safety and efficacy of combinations of CAVERJECT and other vasoactive agents have not been systematically studied. Therefore, the use of such combinations is not recommended.
7. CAVERJECT IMPULSE uses a superfine (29 gauge) needle. As with all superfine needles, the possibility of needle breakage exists. Careful instruction in proper patient handling and injection techniques may minimize the potential for needle breakage.
8. The patient should be instructed not to re-use or to share needles or syringes. As with all prescription medicines, the patient should not allow anyone else to use his medicine.

Information for the Patient:

To ensure safe and effective use of CAVERJECT, the patient should be thoroughly instructed and trained in the self-injection technique before he begins intracavernosal treatment with CAVERJECT at home. The desirable dose should be established in the physician's office.

Any reconstituted solution with precipitates or discoloration should be discarded. The CAVERJECT IMPULSE syringe system is designed for one use only and should be discarded after use. The delivery system and the needle must be properly discarded after use. Needles must not be re-used or shared with other persons. Patient instructions for administration are included in each package of CAVERJECT IMPULSE.

The dose of CAVERJECT that is established in the physician's office should not be changed by the patient without consulting the physician. The patient may expect an erection to occur within 5 to 20 minutes. A standard treatment goal is to produce an erection lasting no longer than 1 hour. Generally, CAVERJECT should be used no more than 3 times per week, with at least 24 hours between each use.

Patients should be aware of possible side effects of therapy with CAVERJECT; the most frequently occurring is penile pain after injection, usually mild to moderate in severity. A potentially serious adverse reaction with intracavernosal therapy is priapism. Accordingly, the patient should be instructed to contact the physician's office immediately or, if unavailable, to seek immediate medical assistance if an erection persists for longer than 4 hours.

The patient should report any penile pain that was not present before or that increased in intensity, as well as the occurrence of nodules or hard tissue in the penis to his physician as soon as possible. As with any injection, an infection is a possibility. Patients should be instructed to report to the physician any penile redness, swelling, tenderness or curvature of the erect penis. The patient must visit the physician's office for regular check-ups for assessment of the therapeutic benefit and safety of treatment with CAVERJECT.

Note: Use of intracavernosal CAVERJECT offers no protection from the transmission of sexually transmitted diseases. Individuals who use CAVERJECT should be counseled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV).

The injection of CAVERJECT can induce a small amount of bleeding at the site of injection (see ADVERSE REACTIONS section hematoma, ecchymosis, hemorrhage at the site of injection). In patients infected with blood-borne diseases, this could increase the risk of transmission of blood-borne diseases between partners.

In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or non-steroidal anti-inflammatory drugs had no effect on the efficacy or safety of CAVERJECT.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Long-term carcinogenicity studies have not been conducted. Rat reproductive studies indicate that alprostadil at doses of up to 0.2 mg/kg/day does not adversely affect or alter rat spermatogenesis, providing a 200-fold margin of safety compared with the usual human doses. The following battery of mutagenicity assays revealed no potential for mutagenesis: bacterial mutation (Ames), alkaline elution, rat micronucleus, sister chromatid exchange, CHO/HGPRT mammalian cell forward gene mutation, and unscheduled DNA synthesis (UDS).

A 1-year irritancy study was conducted in three groups of 5 male Cynomolgus monkeys injected intracavernosally twice weekly with either vehicle or 3 or 8.25 mcg of alprostadil/injection. An additional two groups of 6 monkeys each were injected with vehicle or with 8.25 mcg/injection twice weekly as described previously plus they received multiple doses during weeks 44, 48, and 52. Three monkeys from each group were retained for a 4-week recovery period. There was no evidence of drug-related penile irritancy or nonpenile tissue lesions, which could be directly related to alprostadil. The irritancy, which was noted for control and treated monkeys, was considered to be a result of the injection procedure itself, and any lesions noted were shown to be reversible. At the end of the 4-week recovery period, the histological changes in the penis had regressed.

Pregnancy, Nursing Mothers, and Pediatric Use:

CAVERJECT is not indicated for use in pediatric patients or women.

Geriatric Use:

A total of 341 subjects included in clinical studies were 65 and older. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and the other reported clinical experience has not identified differences in responses between elderly and younger patients, but decreased sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Local Adverse Reactions: The following local adverse reaction information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

Local Adverse Reactions Reported by ≥ 1% of Patients Treated with CAVERJECT Sterile Powder for up to 18 Months*

Event	CAVERJECT N = 1861
Penile pain	37%
Prolonged erection	4%
Penile fibrosis**	3%
Injection site hematoma	3%
Penis disorder***	3%
Injection site ecchymosis	2%
Penile rash	1%
Penile edema	1%

* Except for penile pain (2%), no significant local adverse reactions were reported by 294 patients who received 1 to 3 injections of placebo.

** See General Precautions.

*** Includes numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, penile skin tear, strange feeling of penis, discoloration of penile head, itch at tip of penis.

Penile Pain: Penile pain after intracavernosal administration of CAVERJECT was reported at least once by 37% of patients in clinical studies of up to 18 months in duration. In the majority of the cases, penile pain was rated mild or moderate in intensity. Three percent of patients discontinued treatment because of penile pain. The frequency of penile pain was 2% in 294 patients who received 1 to 3 injections of placebo.

Prolonged Erection/Priapism: In clinical trials, prolonged erection was defined as an erection that lasted for 4 to 6 hours; priapism was defined as erection that lasted 6 hours or longer. The frequency of prolonged erection after intracavernosal administration of CAVERJECT was 4%, while the frequency of priapism was 0.4% (see WARNINGS).

Hematoma/Ecchymosis: The frequency of hematoma and ecchymosis was 3% and 2%, respectively. In most cases, hematoma/ecchymosis was judged to be a complication of a faulty injection technique. Accordingly, proper instruction of the patient in self-injection is of importance to minimize the potential of hematoma/ecchymosis.

The following local adverse reactions were reported by fewer than 1% of patients after injection of CAVERJECT: balanitis, injection site hemorrhage, injection site inflammation, injection site itching, injection site swelling, injection site edema, urethral bleeding, penile warmth, numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, painful erection, and abnormal ejaculation.

Systemic Adverse Events: The following systemic adverse event information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

Systemic Adverse Events Reported by ≥ 1% of Patients Treated with CAVERJECT Sterile Powder for up to 18 Months*

Body System/Reaction	CAVERJECT N = 1861
Cardiovascular System	
Hypertension	2%
Central Nervous System	
Headache	2%
Dizziness	1%
Musculoskeletal System	
Back pain	1%
Respiratory System	
Upper respiratory infection	4%
Flu syndrome	2%
Sinusitis	2%
Nasal congestion	1%
Cough	1%
Urogenital System	
Prostatic Disorder**	2%
Miscellaneous	
Localized pain***	2%
Trauma****	2%

* No significant adverse events were reported by 294 patients who received 1 to 3 injections of placebo.

** Prostatitis, pain, hypertrophy, enlargement

*** Pain in various anatomical structures other than injection site

**** Injuries, fractures, abrasions, lacerations, dislocations

The following systemic events, which were reported for < 1% of patients in clinical studies, were judged by investigators to be possibly related to use of CAVERJECT: testicular pain, scrotal disorder, scrotal edema, hematuria, testicular disorder, impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension, vasodilation, peripheral vascular disorder, supraventricular extrasystoles, vasovagal reactions, hypesthesia, non-generalized weakness, diaphoresis, rash, non-application site pruritus, skin neoplasm, nausea, dry mouth, increased serum creatinine, leg cramps, and mydriasis.

Hemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed during clinical studies, principally at doses above 20 mcg and above 30 mcg of alprostadil, respectively, and appeared to be dose-dependent. However, these changes were usually clinically unimportant; only three patients discontinued the treatment because of symptomatic hypotension.

CAVERJECT had no clinically important effect on serum or urine laboratory tests.

The safety of CAVERJECT IMPULSE was evaluated in a study that compared the formulation of alprostadil for injection contained in CAVERJECT IMPULSE with the formulation contained in CAVERJECT Sterile Powder. The doses used by the 87 patients in this crossover study were the same for both formulations. The number and type of events reported for CAVERJECT IMPULSE were consistent between formulations in this study and in other controlled and uncontrolled studies with CAVERJECT Sterile Powder.

Post-Marketing Surveillance: The following additional adverse reactions have been reported: device malfunction/failure, drug ineffective and drug effect decreased.

OVERDOSAGE

Overdosage was not observed in clinical trials with CAVERJECT. If intracavernous overdose of CAVERJECT occurs, the patient should be under medical supervision until any systemic effects have resolved and/or until penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.

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PREPARE

continued from page 39

learn and understand the codes, Dr. Terry says.

A glitch waiting to happen?

Even the government is planning on problems with ICD-10 implementation. In a February 2014 press release, the AMA referred to an estimate by the Centers for Medicare & Medicaid Services that claims denial rates could increase 100% to 200% in the early stages of coding with ICD-10.

Every step in the process, including practice EMRs, clearinghouses, and payers, is vulnerable to system glitches.

"One of my fears when ICD-10 comes to fruition is the potentially significant delay in payments from insurance companies. The insurance companies, themselves, need to know more than 68,000 codes to make sure they code correctly," Dr. Rubenstein said. "The problem with practices is they need to get prepared for the potential of very little money coming into the practice starting on Oct. 1, 2015, until everyone is caught up on using ICD-10."

That's easier said than done. And if the rollout of Obamacare is any indication, urologists and others could experience problems with reimbursement beginning Oct. 1, according to Dr. Terry.

"[ICD-10] was supposed to be implemented Oct. 1, 2013. That happened to be the same day the Obamacare exchanges went online. If we had really had ICD-10 implemented on that day, I can't imagine how many doctors would be out of business," Dr. Terry said.

Even a month without income puts the viability of doctors' offices in jeopardy, according to Dr. Terry, who practices in a seven-physician practice, which is considered medium sized. Dr. Terry says he has heard that physicians will need 4 to 6 months of money set aside to weather the transition.

"You can't get a loan or line of credit big enough. It would be an unsecured loan. Most doctors rent their buildings—they don't have any assets," Dr. Terry said. "My office needs to come close to $1 million a month to run, so if I need 4 months of income, that's $4 million. We don't have that."

Dr. Terry says at least he is confident that his practice will be prepared for ICD-10. What he says he really worries about is the one- and two-doctor practices in rural America. "They don't know what's about to hit them," he said.

No more delays?

Initially, ICD-10 was scheduled to launch Oct. 1, 2013. The first delay pushed it to Oct. 1, 2014; the second delay, to 2015.

"There's no good reason to believe that it will be pushed back any further. Many, including hospital systems and insurance companies that had previously invested heavily in preparing for ICD-10 for Oct. 1, 2014, made a lot of grumbling about the delay," Dr. Rubenstein said.

Dr. Terry, however, says ICD-10 is not ready for prime time and needs to be delayed for another 5 years in order to fix it appropriately.

What physicians might not know is that the argument the U.S. is lagging behind other countries, such as Canada, in transitioning to ICD-10 is misleading.

"We're the only country that's going to implement the full 68,000 to 85,000 codes. Canada only implemented approximately 20,000 codes," Dr. Terry said.

Another notable difference is that the U.S. is the only country that couples the ICD code

ICD-10 RESOURCES ONLINE

The following resources are available at bitly.com/UT-ICD10-resources.

- **"Road to 10."** An overview of ICD-10, with webcasts, FAQs, and more
- **ICD-10 Resource Center.** Multiple links and resources from sister publication *Medical Economics*
- **ICD-10 implementation timelines.** Timelines from CMS for small, medium, and large practices
- **ICD-10 preparation:** A printable checklist for urologists to ensure your practice is on track
- **AUA training.** Basic training and other resources for urologists
- **ICD-10 webinars, live seminars.** From PRS Urology; starting in April 2015

with physician reimbursement, according to Dr. Terry.

"The whole purpose of ICD, from the very beginning, was for statistical and epidemiological data, not to be coupled with billing codes. But insurance companies use these ICD-10 codes to deny payments to doctors; so does Medicare," Dr. Terry said. "And we're the only country that uses these codes in the outpatient setting. That's where most of the care is—in your office—in the outpatient setting. Other countries just use it for hospital patients."

Dr. Terry says his plan is to work with others in Congress to achieve another delay, legislatively. His goal is for a 5-year delay to focus on and fix the problem of a flawed implementation plan and too many codes (see, "Possible fixes," page 39).

"I agree we need to have an updated coding system, but we must do it the right way so as not to put physicians out of business and disrupt patient care," he said.

Armageddon or a blip?

Mark Painter says a lot of physicians fear ICD-10 is Armageddon.

"I really feel that this is a digestible change. If you walk through this process and work with the right IT folks and vendors, and you've selected well, system-wise, the transition is not going to be that overwhelming. Luckily, urologists are not in the specialties of OB/Gyn or orthopedics," Painter said. "The payers, while they have the potential of tightening up rules and adding new requirements, don't appear to be going in that direction. So, I think the overall process probably won't be as bad as everyone thinks."

According to Dr. Terry, ICD-10 is not a urology issue. It's an across-the-board issue for medicine and the future of the profession itself.

"Patient care is what I want to stress. It's a lot more than urology or surgery. The [message] is how flawed this ICD-10 system and implementation process is—how it's going to adversely affect our profession and the care of our patients," Dr. Terry said. UT

ICD-10 progress slows among small practices

Small practices have slowed in their preparation for the implementation of the International Classification of Diseases 10th revision (ICD-10), according to a recent survey from the Workgroup for Electronic Data Interchange (WEDI).

Originally scheduled to launch this year, the switch to the ICD-10 code set was delayed until Oct. 1, 2015. But it seems the extra time has allowed for many providers to delay their preparation efforts.

The survey found that only about half of providers have conducted impact assessments, which is consistent with what they reported in the 2013 WEDI survey. While four-fifths of large practice providers have completed assessments, about 75% of smaller practice providers said they do not know when they plan to complete an assessment or that it has been delayed until 2015.

About one-third of providers reported that they have begun external testing, while more than 50% said they plan to wait until 2015 or do not know when they will conduct testing. Only one-eighth of providers reported that the delay in ICD-10 did not impact their preparation timeline.

The WEDI survey had 514 respondents, which included 324 providers, 87 vendors, and 103 health plans.

Wearable coil facilitates positioning during prostate MRI

Omaha, NE—ScanMed of Resonance Innovations LLC has introduced a wearable MRI coil designed for visualizing the prostate and reproductive organs while also allowing for biopsy. The PROCURE (Prostate, Rectum, Ovaries, Cervix, Uterus, Reproductive) is a wearable, stain-resistant, and fluid-proof coil that facilitates accurate positioning, according to ScanMed. Similar to wearing a diaper, the device positions the multiple antenna elements as close as possible to the target anatomies regardless of patient size. The enclosure for the antenna set is made of flexible liquid-impermeable, biocompatible materials. Disposable liners are included so the coil can be changed between patients.
For more information, visit *www.scanmed.com.*

16-slice CT scanner suitable for urology practices

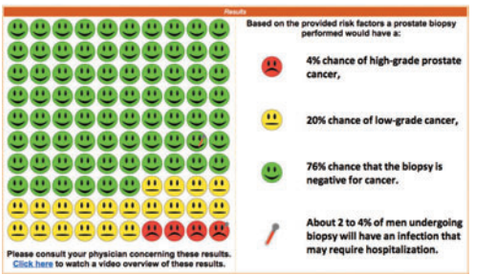
Malvern, PA—The FDA has cleared Siemens Healthcare's SOMATOM Scope, a 16-slice computed tomography scanner. Suitable for urology and other specialty practices, the SOMATOM Scope is available in two configurations—Scope and Scope Power—and enables providers to comply with the NEMA XR-29 Smart Dose Standard to ensure safer imaging. It also includes eCockpit technology that extends operational lifetime by minimizing wear and tear on vital components.
For more information, visit *http://usa.healthcare.siemens.com/.*

New generic testosterone gel available in three configurations

Maple Grove, MN—Upsher-Smith has launched a generic version of Vogelxo testosterone gel (1%) for topical use in the treatment of adult males who have low or no testosterone and with conditions associated with low or no testosterone. The generic testosterone gel offers once-daily dosing, 24-hour coverage, and three configurations: unit-dose tubes, packets, and metered-dose pumps.

For more information, visit *www.upsher-smith.com.*

Prostate cancer risk calculator updated with current risk factors



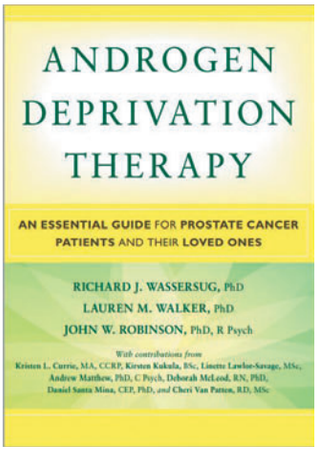
San Antonio—The University of Texas Health Science Center has upgraded its prostate cancer risk calculator, which helps men and their physicians better understand a man's risk of prostate cancer. The version 2.0 calculator has been updated to use current risk factors and a better interface. The free calculator takes minutes to use and gives a man more information about his risk for both low-grade prostate cancer, which may never require treatment, and high-grade prostate cancer. It uses an "emoji" graphic readout that puts the numeric percentages into a visual perspective and gives the possibility in numbers (and emojis) that a patient may have no prostate cancer at all.
For more information, visit *http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp.*

FDA clears home-use conception assistance device

Pittsburgh—The Stork OTC is a new home-use conception assistance device that has been cleared by the FDA for over-the-counter sales. The device provides consumers a safe, easy way to perform cervical cap insemination at home, according to Rinovum Women's Health. The Stork includes two parts: an updated cervical cap (similar to a condom) and an applicator device used to place the cap (similar to the delivery of a tampon). After collecting semen in the cap during natural intercourse, the applicator places it near the woman's cervix. The cap stays in place, keeping sperm where it needs to be for up to 6 hours, while the woman continues her normal routine, then is easily removed with the attached cord.

For more information, visit *www.storkotc.com.*

Guide helps prostate cancer patients cope with androgen deprivation



New York—Demos Health has published "Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones," which is designed to help patients cope with ADT and increase their quality of life. The book discusses the physical side effects of hormone therapy and how to manage them, how to navigate emotional side effects, and ways partners can maintain sexual pleasure. It also offers an activity worksheet for each chapter that includes goal-setting charts, side effect self-assessments, and personal action plans.
For more information, visit *www.demoshealth.com.*

Clinical manual is practical guide to daily urology practice

Philadelphia—The "Penn Clinical Manual of Urology," now in its second edition, is designed to be a concise, practical guide to the daily practice of urology. This edition covers the latest incontinence guidelines from the AUA and International Consultation on Incontinence, current treatment recommendations, therapy for castrate-resistant prostate cancer, and active surveillance for prostate cancer. It includes chapters on major categories of urologic diseases, helps readers prepare for board examinations, and is entirely searchable online.
For more information, visit *www.us.elsevierhealth.com.*

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Prostate cancer council bill earns AUA support

AUA also urging passage of USPSTF transparency legislation

Bob Gatty
UT Washington Correspondent

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

Washington—The effort to draw attention to the importance of prostate cancer detection was given a big boost in September when conservative Sen. Jeff Sessions (R-AR) and liberal Sen. Barbara Boxer (D-CA) joined together to sponsor legislation to create the National Prostate Cancer Council.

According to a statement by the two lawmakers, the council's mission would be to develop and carry out a national strategy to improve screening, assessment, early detection, and monitoring of prostate cancer.

"Testing and early detection are the keys to combat this disease. When identified early, the survival rate for prostate cancer is very high. We need to ensure that we have the most advanced screening tools available, and this legislation is a step in the right direction," said Sessions, a prostate cancer survivor.

"Prostate cancer is one of the leading threats to the health and lives of the men of this country," Boxer said. "We owe it to our families to do all we can to fight this deadly disease."

Would coordinate research efforts

The council, should it be created by Congress, would be charged with developing a national plan for accelerated creation of diagnostic tools; providing information and coordination of prostate cancer research and services among the federal agencies; reviewing the current diagnostic tools and their effectiveness; evaluating all prostate cancer programs, including federal budget requests; reporting to both the U.S. Department of Health and Human Services and Congress; and ensuring that high-risk men be included in any strategy.

Boxer is no newcomer to the effort to improve prostate cancer detection. In 2012, she and Rep. Elijah Cummings (D-MD) sponsored the Prostate Cancer Detection Research and Education Act, intended to improve research and detection of prostate cancer.

"The goals for the council outlined in S. 2813—such as improving prostate cancer screening and early detection—very much align with the AUA's advocacy priorities."

DAVID F. PENSON, MD, MPH

That measure would have increased federal funding for prostate cancer research. It called for a panel of leading medical experts to be created to work toward the ultimate goal of developing an accurate test that can detect prostate cancer and diagnose its severity.

The AUA said it supports the new Sessions-Boxer bill, S. 2813.

"Although this measure was just introduced, the goals for the council outlined in S. 2813—such as improving prostate cancer screening and early detection—very much align with the AUA's advocacy priorities," said David F. Penson, MD, MPH, the AUA's Public Policy Council chair. He said the AUA "would be encouraged" to see the bill "gain bipartisan traction during the remainder of the 113th Congress."

Approval urged for USPSTF legislation

The AUA is also urging approval of legislation sponsored by Sen. Deb Fischer (R-NE), the Healthy Families Act of 2014, which would make the U.S. Preventive Services Task Force (USPSTF) more transparent and open to the public. The AUA is asking members to help garner lawmaker support for the senator's bill, S. 2574.

It was the USPSTF in 2012 that recommended against the use of PSA testing in all men. In 2013, AUA issued new guidelines that support the use of PSA in a "more targeted manner," but says that all men ages 55 to 69 years who are in good health and have more than a 10- to 15-year life expectancy "should have the choice to be tested and not discouraged from doing so."

The AUA also noted in its guidelines that the USPSTF panel that developed the 2012 recommendations did not include representation from the urology community.

"As the physicians most experienced in the diagnosis and treatment of prostate cancer, we feel that urologists should be involved in the development of prostate cancer screening recommendations to ensure that the guidance is evidence-based and also targets the preferences of individual patients," the AUA said in its guideline document.

The AUA, of course, has been an ardent supporter of prostate cancer detection initiatives and research, and on Sept. 18 Dr. Penson wrote to senators urging their support for passage of Sessions' resolution designating September 2014 as "National Prostate Cancer Awareness Month."

"The AUA strongly supports this resolution, which declares that steps should be taken to raise awareness about the importance of prostate cancer screening methods and treatments, to increase prostate cancer research funding, and to improve access to and quality of health care services for detecting and treating prostate cancer," Dr. Penson wrote.

The resolution, which was passed unanimously by the Senate, also called on the nation to take an active role in promoting prostate cancer awareness "and the fight to end the devastating effects of prostate cancer," said Dr. Penson.

"Educating people about prostate cancer and early detection strategies is crucial to saving the lives of these men, and ongoing research can improve prostate cancer prevention, early detection, and treatment. We applaud Senator Jeff Sessions and encourage you to join him in supporting this resolution to further prostate cancer awareness," Dr. Penson added. UT

Fast Facts

The proposed National Prostate Cancer Council:

- is a bipartisan measure sponsored by conservative Sen. Jeff Sessions (R-AR) and liberal Sen. Barbara Boxer (D-CA)
- would be tasked with developing and carrying out a national strategy to improve screening, assessment, early detection, and monitoring of prostate cancer
- would also be charged with developing a national plan for accelerated creation of diagnostic tools
- is supported by the AUA

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

MEN'S HEALTH

Shock wave therapy could be used to treat erectile dysfunction

THE NEXT GREAT ADVANCEMENT in erectile dysfunction treatment since sildenafil citrate (Viagra) could be shock wave therapy, *Men's Health* says.

Previous research indicates that shock waves to the heart can help new blood vessels form to treat heart problems, and physicians believe the same method can be used to alleviate ED caused by restricted blood flow. Researchers use a wand attached to a machine to send small shocks directly to the penis.

"It emits energy that increases growth factor levels, which in turn produce new blood vessels," said Vijay Sangar, BSc, MBChB, MD, of Spire Manchester Hospital, Manchester, the United Kingdom.

The ED1000 Therapy was developed in Israel and is not available in the United States.

MEDSCAPE

Study: Renal cell carcinoma on the rise among children, teens

THE OVERALL RATE OF CANCER in American children and teens remained stable during the last 10 years, but the rate of kidney cancer increased, according to a study in *Pediatrics* (2014; 134:e945-55).

Renal cell carcinoma in this population had an average increase of 5.4% per year. Study authors also found that overall cancer rates among African-American children and teens increased 1.3% per year.

5.4%
INCREASE PER YEAR IN RCC AMONG TEENS, KIDS

"This is the first time that we are aware renal carcinoma is also increasing in children," lead researcher David Siegel, MD, MPH, of Children's Healthcare, Atlanta, told *Medscape Medical News*.

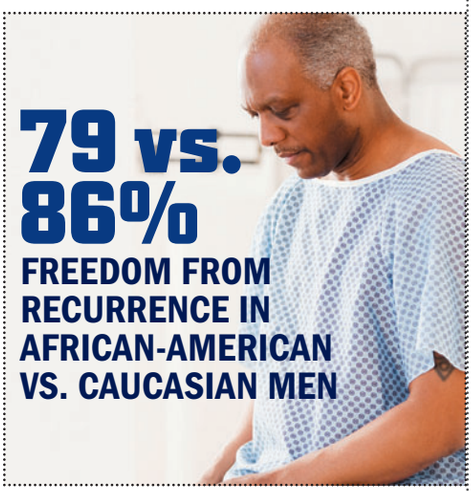
While the direct cause of this increase is not known, "In adults, there has been an association between kidney cancer and obesity, but again, we don't know if obesity is causal," Dr. Siegel added.

HEALTHDAY NEWS

Watchful waiting may not be suitable for African-American PCa patients

MONITORING early-stage prostate cancer instead of treating it may not always be the best choice, especially in African-American men, according to a recent study.

"Our study shows that African-American men who are diagnosed with a low-grade cancer at first—the cancers that are sometimes watched rather than treated—are more likely to develop aggressive disease sooner than Caucasian men," said first author Kosj Yamoah, MD, PhD, of Thomas Jefferson University, Philadelphia.



Dr. Yamoah and colleagues analyzed medical records of men who were confirmed to have low-grade prostate cancer and underwent prostatectomy. Of these, African-American men were more likely to have cancer progression. At 7 years post-surgery, the overall freedom from biochemical recurrence rate was 86% in Caucasian men versus 79% in African-American men, as reported online in *Urologic Oncology* (Oct. 9, 2014).

NPR

Proton beam radiation Tx centers growing despite closure of one clinic

PROTON BEAM radiation therapy centers continue to grow in number, despite a recent announcement that Indiana University plans to close its center.

In the Washington, DC area, three centers are currently under construction. But at Indiana University, a review committee determined it was not worth updating that institution's facility. One reason cited for the closure is that insurers have been refusing to cover the treatment for common diseases, including prostate cancer.

The three institutions currently building proton beam RT centers said that construction would continue as planned, despite the closure of Indiana's center.

PHOTO: GETTY IMAGES/BLEND IMAGES

NEWS **ODDITIES**

Man suffers from spontaneous, persistent orgasms

A WISCONSIN MAN is suffering from up to 100 unwanted orgasms every day, a condition known as persistent genital arousal syndrome.

"There's nothing pleasurable about it, because even though it might physically feel good, the whole time inside your mind, you're completely disgusted by what's going on," said Dale Decker, who suffers from spontaneous and persistent orgasms unrelated to any physical stimulus or feelings of sexual arousal.

Decker first began suffering in 2012 after slipping a disk in his back, according to a report from CBS Chicago. While on his way to the hospital, he had five unwanted orgasms. They have continued on a regular basis since then.

"When you're on your knees at your father's funeral… and then you have nine orgasms right there while your whole family is standing behind you, you never want to have another orgasm as long as you live," he said.

Decker said that he has been unable to work since the accident, and he is also mostly housebound out of fear of experiencing an orgasm in public.

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