Brian Jumper, MD, is employed by Maine Medical Partners Urology, which is part of Maine Medical Center in Portland and part of the state-wide Maine Health hospital system. Dr. Jumper has been in hospital-based practice as a full-time faculty member in Maine Medical Center’s urology residency program for 7 years. Before that, he was in private practice for 19 years.

Michael Fabrizio, MD, CEO of the 30-urologist group Urology of Virginia, joined a health system in Virginia in 2008 amid what he calls an acquisition war between rival hospitals. Dr. Fabrizio said becoming employed seemed logical at the time, given his concerns about the complex and costly administrative aspects of remaining in private practice, such as electronic medical.
AN EPIGENETIC ASSAY TO IMPROVE PATIENT STRATIFICATION ON THE DECISION FOR REPEAT BIOPSY

THE MOST SIGNIFICANT INDEPENDENT PREDICTOR FOR PROSTATE CANCER DETECTION ON REPEAT BIOPSY \(^{(1,2)}\)

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**The test helps you:**

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- **RULE IN** those who may require repeat biopsies and potential treatment.

**ConfirmMDx Clinical Validity & Utility**

- \(~90\%\) Negative Predictive Value \(^{(1-3)}\)
- Performance of genes and MSP technology published in 45+ studies and tested on \(~5,000\) patients
- Test performed on prior negative biopsy tissue

**ConfirmMDx is the Most Significant Independent Predictor for Prostate Cancer Detection on Repeat Biopsy \(^{(1,2)}\)**

**DOCUMENT Results: Multivariate Analysis of Known Risk Factors and Assay Performance \(^{1}\)**

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Robotics finding a role in prolapse repair

W ith the widespread acceptance of robot-assisted surgery for reconstructive procedures such as radical prostatectomy and partial nephrectomy, the next frontier for urologist robot-assisted surgery appears to be in the female pelvis.

A group of fellowship-trained surgeons from Beaumont Hospital in Royal Oak, MI recently reported their considerable experience with robotically assisted pelvic organ prolapse repair, which is highlighted in this issue of Urology Times (see article, page 6). Among the 197 procedures, almost all were sacrocolpopexy. Most patients were discharged from the hospital the day after surgery.

The intra-operative complication and early postoperative complication rates were quite acceptable. There was a 21% rate of grade 2 or 3 recurrent pelvic organ prolapse, but only a 4.8% rate of repeat repair. Despite being an abdominal (as opposed to vaginal) procedure, there was still a mesh exposure rate of 9.8%. It is reassuring to note, however, that fewer than half of the patients with mesh exposure required surgical revision.

It was hoped that the abdominal approach might reduce the rate of mesh complications compared to a vaginal approach, but this does not appear to be the case. Although the FDA warning about mesh for pelvic organ prolapse repair pertains to transvaginal use, appropriate counseling of patients before any use of mesh is encouraged.

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There certainly appears to be a role for robot-assisted pelvic organ prolapse repair, but long-term studies are vital to assess the best role for this procedure.

J. Stuart Wolf, Jr, MD

Dr. Wolf, a member of the Urol- ogy Times Editorial Council, is the David A. Bloom Professor of Urology and associate chair for surgical services at the University of Michigan, Ann Arbor.
Another Obamacare legal challenge picks up steam

LEGISLATIVE UPDATE

This summer, the Supreme Court ruled that the Affordable Care Act guarantees subsidies to individuals regardless of whether they live in a state that has established exchanges. “Any changes to the law will need to be made at the legislative level,” Kevin R. Loughlin, MD, MBA, wrote in a Urology Times article shortly thereafter. Dr. Loughlin’s words may be prophetic. A new challenge has even the most ardent ACA supporters nervous, writes Dan Shaffer of the AACU.

READ DR. LOUGHLIN’S ANALYSIS AT urologytimes.com/supremecourt
AND SHAFFER’S UPDATE AT urologytimes.com/challenge

In the past year, how has your stress level at work changed?

OCTOBER’S QUESTION OF THE MONTH

What has been your reaction to ICD-10 since Oct. 1?

About what I expected 48%

Better than expected 24%

Worse than expected 28%

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Video: The consequences of delaying stone treatment

A University of Texas Southwestern Medical Center study found longer time intervals between diagnosis and treatment of kidney stones is associated with increased patient morbidity and more frequent use of imaging and antibiotics. Hear one expert’s reaction.

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Royal Oak, MI—A robot-assisted abdominal approach to pelvic organ prolapse repair has a favorable safety profile and is associated with durable anatomic outcomes, findings of a retrospective chart review indicate.

**Female Urology**

Women underwent the procedure at a large teaching institution, Beaumont Hospital in Royal Oak, MI.

The series included 197 consecutive women operated on between 2007 and 2014 by surgeons with fellowship training in female pelvic medicine and reconstructive surgery. With the exception of six women (3%) who had a hysterectomy and one woman (0.5%) who had enterocle repair, all of the other procedures were sacrocolpopexy. Follow-up for the cohort averaged almost 14 months; 187 women had documented exams at 1 month and 123 women had follow-up beyond 6 months.

Analyses of the extracted data showed most operative and postoperative complications were minor. The rate of anatomic failure, defined by presence of grade 2 or 3 prolapse on follow-up, was about 24%, and when considering only women followed longer than 6 months, the mesh exposure rate was 9.8%, reported first author Michael Ehler, MD, at the AUA annual meeting in New Orleans.

“We believe this study comprises the largest series on robotic prolapse repair and that it provides better insight than previous reports about the complications, especially in terms of the nuances of an abdominal approach,” said Dr. Ehler, formerly a female pelvic medicine and reconstructive surgery fellow at Beaumont Hospital who now is in practice in Minneapolis.

“The anatomic outcome in our cohort is similar to that reported during long-term follow-up in the NIH-sponsored study of open abdominal sacrocolpopexy [JAMA 2013; 309:2016-24]. Our mesh exposure rate is similar as well, underscoring that this problem is not avoided with an abdominal approach. While we found that the complications associated with the procedure were minor overall, the rates were higher than in previous reports, and we attribute that to our careful chart review.”

MICHAEL EHLENT, MD

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**InBrief**

**Study details racial discrepancies in PCa care**

Older African-American men with localized prostate cancer were more likely to have poorer quality care, incur higher costs, and have worse postoperative outcomes than Caucasian men, but that did not translate to worse overall or cancer-specific survival, according to a recently published study.

For the study, which was published online in *JAMA Oncology* (Oct. 22, 2015), Quoc-Dien Trinh, MD, of Brigham and Women’s Hospital, Harvard Medical School, Boston, and co-authors looked at the effect of race on quality of care and survival of men receiving radical prostatectomy for localized prostate cancer. They used data from the Surveillance, Epidemiology and End Results-Medicare database for 26,482 men 65 years of age or older who underwent RP: 2,020 African-American men and 24,462 non-Hispanic Caucasian men.

Among their findings were that 59.4% of African-American men underwent RP within 90 days versus 69.5% of Caucasian men; African-American men had a 7-day treatment delay compared with Caucasian men in the top 50% of patients; African-American men were less likely to undergo lymph node dissection; and African-American and Caucasian men had similar cancer-specific and overall death rates.
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Pelvic floor muscle training app provides biofeedback

Patients give app high marks on ease of use, usefulness in improving Kegels

Cheryl Guttman Krader
UT Concepting Editor

San Francisco—A smartphone app for pelvic floor muscle training has valuable potential as a portal to patient care and education and for facilitating clinical outcomes research, according to its developers from the University of California, San Francisco.

Known as “Kegel Nation,” the app was created by Maurice Garcia, MD, and Peter Carroll, MD, to provide real-time biofeedback to patients performing pelvic floor muscle training. As a platform for collecting a variety of data, however, it can also serve as a clinical interface for physicians to track patient progress and relay treatment-related information. In addition, the app can be used as an instrument for collecting research data.

An initial assessment of the app, which was conducted in 10 non-medical subjects, validated its accuracy for recording the duration of muscle contraction and relaxation during Kegel exercises. Participant feedback about the app was also very positive.

“Kegel exercises are best coupled with biofeedback early on so that patients know they are doing the exercises correctly. To date, however, assessment of the duration of contraction is only feasible with in-office biofeedback. Furthermore, the efficacy of Kegel exercises also depends on the number of exercises completed, but we have observed that many patients do not reliably track that information,” said Dr. Garcia, assistant clinical professor in residence in the UCSF department of urology.

“As smartphones are ubiquitous and patients are comfortable using them, we hypothesized that a smartphone app giving feedback on parameters of Kegel exercise could be effective for improving outcomes. In addition, we expect it could serve as an interface platform for research and patient education.”

The app is scheduled to launch on iTunes and will also be available for Android users. The data collection for the public version of the app reflects Kegel contraction and active relaxation duration, which is recorded with tactile feedback from the user interfacing with a “button” that appears on the screen. Users can also enter information on urinary urgency, voiding, and urinary incontinence events and number of pads used. There is also a questionnaire element that records responses using a visual analogue scale.

The initial validation study enrolled men and women ages 40 to 70 years who were asked to complete 10 Kegel exercises using the app to measure contraction/relaxation duration. The contraction and relaxation times were recorded simultaneously with a stopwatch. Across all 10 subjects, there was <1 second difference between the Kegel contraction and relaxation times recorded using the two methods.

Positive feedback from users
Users were also queried about the ease of using the app, its usefulness for improving Kegel performance, and anxiety related to using wireless technology for transmitting their personal data for research purposes. Mean score for ease of use was 9.4 out of a best possible 10, and the participants’ responses to the other questions showed they had a very low level of privacy-related anxiety (mean score, 9.1) and considered the app to have a high degree of usefulness (mean score, 9.8).

“As a limitation, our study enrolled all healthy volunteers. As pelvic floor muscle training has been shown to improve time to return of continence following radical prostatectomy, we will be implementing a research version of the app in a randomized controlled trial of men who are recovering from radical prostatectomy,” Dr. Garcia said.

The research app interfaces with a HIPAA-compliant server that collects the encrypted data remotely in real time.

Michael Leapman, MD, a urologic oncology fellow at UCSF, presented the project on behalf of Drs. Garcia and Carroll at the AUA annual meeting in New Orleans.

PROLAPSE REPAIR

reported in previous robotic series, and the majority of women were discharged on the first postoperative day.

13 intraoperative complications observed

Intraoperatively, there were 13 complications, including four cases each of cystotomy and vaginotomy that were repaired primarily, two conversions to an open procedure, two aborted procedures, and one case where the ureter was sutured by the gynecology team.

The only pre-op or operative difference noted in women with an intraoperative complication was a slightly, but significantly higher estimated blood loss.

The Clavien-Dindo system was used to classify complications. There were 18 early complications (within 30 days), of which 16 were Clavien I or II (UTI, constipation). The two Clavien IIIb complications requiring a return to the OR involved a woman with a port site hernia on post-op day 2 and the patient with a suture in the ureter, which was easily removed endoscopically.

There were 36 late complications, three-fourths of which were Clavien I. Of the 12 mesh exposures, five were managed surgically, while the majority were either observed or treated with topical estrogen. Average time to mesh excision was 9 months.

Anatomic outcomes were analyzed among the 187 women who had at least 4 weeks follow-up. At last follow-up, the prolapsed grade was 0 in 100 women (53.5%), grade 1 in 47 women (25.1%), grade 2 in 26 women (13.9%), and grade 3 in 14 women (7.5%). The grade 3 cases were equally divided between anterior and posterior prolapse.

“We had no cases of recurrent apical prolapse, and the majority of anterior and posterior compartments were not symptomatic requiring surgery,” Dr. Ehlert said.

Nine of the 14 women with a grade 3 prolapse underwent surgery for their recurrence at a mean of 9.5 months. A number of clinical and operative variables were analyzed for their possible association with recurrence, including age, body mass index, hysterectomy, and prior prolapse repair, but none was found to be an independent predictor.
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Botulinum efficacious long term for neurogenic bladder
Consistent reduction in incontinence episodes seen over 4-year period

Benjamin P. Saylor
CONTENT MANAGING EDITOR

Charleston, SC—OnabotulinumtoxinA (Botox) appears to offer long-term benefits in patients with neurogenic detrusor overactivity, recent study results indicate.

Previous studies have demonstrated botulinum’s safety and efficacy in patients with neurogenic detrusor overactivity, explained first author Eric Rovner, MD, professor of urology at the Medical University of South Carolina, Charleston. For the current study, which was presented at the AUA annual meeting in New Orleans, Dr. Rovner and colleagues sought to assess long-term outcomes in patients who underwent botulinum treatment for 4 years.

All the patients had urinary incontinence, and all had failed oral drug therapy. Average patient age was about 45 years, and nearly half (45.1%) of the patients were male. At baseline, patients experienced an average of 4.3 urinary incontinence episodes per day, and 71% required clean intermittent catheterization.

Patients had participated in one of two large randomized double-blind placebo-controlled trials evaluating botulinum in doses of 200 U or 300 U that lasted for 1 year. At the conclusion of that study, patients then entered a 3-year extension study. Patients who started on the 300-U dose were switched to 200 U following FDA approval of botulinum, 200 U for treatment of urinary detrusor overactivity.

Patients received up to two treatments in year 1, and then multiple treatments in the 3-year extension phase provided “as needed” for symptom control based on pre-specified retreatment criteria: patient initiation of a request for retreatment, minimum of 12 weeks since previous treatment, and one or more urinary incontinence episodes within 3 days.

Outcomes assessed included change from baseline in number of daily urinary incontinence episodes, proportion of patients with ≥50% and 100% reduction in daily urinary incontinence episodes, overall median duration of effect, rate of adverse events, and initiation of de novo clean intermittent catheterization.

Consistent reduction in incontinence seen
The authors found a consistent reduction in mean number of urinary incontinence episodes per day of –3.4, –3.6, –3.8, and –3.7, over years 1 to 4, respectively. The overall median duration of effect was more than 9 months. In addition, 88%-90% of patients experienced a ≥50% or more reduction in urinary incontinence episodes per day each year of treatment, and 44%-52% of patients reported a 100% reduction in urinary incontinence episodes per day each year of treatment.

“The reduction in incontinence episodes is consistent year to year with repeat injections of onabotulinumtoxinA. The efficacy of the medication does not diminish over time.”
ERIC ROVNER, MD

Botulinum reduces pain in interstitial cystitis, BPS
Hydrogel-based delivery system offers intra-detrusor injection alternative

Chase Doyle
UT CORRESPONDENT

Hualien, Taiwan—Intravesical onabotulinumtoxinA (Botox) reduces bladder pain in patients with interstitial cystitis/bladder pain syndrome (IC/BPS), two separate studies show.

IC/BPS

According to the results of a randomized, controlled trial presented at the AUA annual meeting in New Orleans, botulinum injections improved clinical symptoms, increased bladder capacity, and provided pain relief in patients who were refractory to conventional treatment. “The results of this clinical trial demonstrated that intravesical injection of 100 U Botox effectively reduced bladder pain and increased bladder capacity in patients with IC/BPS refractory to treatment. Rates of adverse events are acceptable and they are manageable,” said Yuan-Hong Jiang, MD, a urologist at Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan.

Although botulinum injections have been demonstrated to be beneficial for the treatment of IC/BPS, therapeutic efficacy has not been validated by a placebo-controlled study. For this trial, the authors recruited IC/BPS patients refractory to conventional treatment.

Sixty patients were randomized in a 2:1 ratio across 20 sites to receive hydrodistention plus intravesical suburothelial injection of botulinum, 100 U, or the equivalent amount of normal saline. The primary endpoint was a decrease in pain assessed using a visual analogue scale (VAS) at week 8 after treatment.

“At week 8,” reported Dr. Jiang, “we observed a significantly greater decrease of VAS in the Botox group compared to the normal saline group. Cystometric bladder capacity and post-void residual urine also showed...
According to Dr. Jiang, the overall success rates were 63% in the botulinum group and 15% in the control. There was no significant difference in the prevalence of adverse events between the groups.

**Slow-release delivery system shows promise**

A separate, pilot study, also presented at the AUA annual meeting, evaluated safety and feasibility of intravesical instillation of Botox in a hydrogel-based slow-release delivery system. That approach also showed promise of pain relief for IC/BPS patients.

“The results of this clinical trial demonstrated that intravesical injection of 100U Botox effectively reduced bladder pain and increased bladder capacity in patients with IC/BPS refractory treatment.”

YUAN-HONG JIANG, MD

The single-arm prospective study included 15 patients (11 females and four males), who received a single intravesical instillation of botulinum, 200 U, premixed with TCGel, 40 mL through a 12F urethral catheter. Median patient age was 48 years, with a body mass index of 26.4 kg/m².

As Dr. Zisman explained, TCGel (TheraCoat Ltd.), instilled as cold fluid at 4°C, solidifies in the bladder within 10 minutes and dissolves gradually in urine.

“An intravesical instillation of a mixture of TCGel and Botox is an appealing alternative to intra-detrusor injection,” he said. “There is an increase in active drug dwell time in the bladder in spite of frequent emptying. Therefore, it acts as a slow-release formulation.”

Bladder pain was measured using a VAS, 3-day bladder diary, and the O’Leary-Sant questionnaire. Assessment was reported prior to installation and 2, 6, and 12 weeks after.

All adverse events were recorded according to study protocol.

“Interestingly,” said Dr. Zisman, “26% of study subjects reported mild constipation. This adverse event was also reported in other studies where Botox was injected into the bladder wall.”

In the entire group study, a significant pain reduction was noted 2 weeks following instillation. A statistically significant reduction in O’Leary-Sant Symptom and Problem Indexes was shown at all checkpoints. There was also tendency for reduction, although not significant, in the mean number of voids per night and in the mean number of urge episodes per day, he reported.

While these findings suggest sustained efficacy, Dr. Zisman concluded that further investigation would require a group being treated with a sham procedure.

Theracoat, Ltd. provided funding for Dr. Zisman’s study. Dr. Zisman’s co-authors are consultants/advisers for or employees of Theracoat.
New York—An initial assessment of robotic ureteral reconstruction using buccal mucosa graft indicates that it is a feasible and reproducible approach for reconstruction of complex ureteral strictures, reconstructive urologists reported at the AUA annual meeting in New Orleans.

Reconstruction

Now, larger and longer experience is needed to optimize the technique and to understand the durability of the outcome, said first author Lee C. Zhao, MD, assistant professor of urology, New York University Langone Medical Center, New York.

“Our goal is to develop a minimally invasive alternative to current techniques for treating long proximal or multifocal ureteral strictures,” he said.

“If we think of where this procedure might fit on the ladder of reconstructive options, robotic ureteral reconstruction using buccal mucosal graft is a nice middle rung for fixing an otherwise difficult problem.”

LEE C. ZHAO, MD

“As these are rare cases, we hope to enlist other centers to join in our multi-institutional study and establish a registry of how the cases are being performed and the outcomes. With that information, we can hone in on the best technique and factors for recurrence.”

Dr. Zhao told Urology Times that the procedure is not technically out of the reach of any surgeon who is proficient in performing upper-tract robotic procedures. He noted, however, that it is nice to work with a team because uroscopy and buccal mucosal harvesting can be done simultaneously.

How the procedure is performed

To perform the procedure, the patient is positioned in a modified lateral decubitus lithotomy position that will enable bladder access, while the mouth is draped separately for harvesting the buccal mucosa graft. Port placement sites are similar to those used for pyeloplasty. Ureterolysis is performed followed by an ureterotomy through the segment of the stricture and suturing of the buccal mucosa graft. The graft can be placed ventrally or dorsally. Omentum is usually used as backing to help perfuse the graft.

Dr. Zhao emphasized the benefit for nephrostomy tube placement and ureteral stent removal preoperatively, which enables accurate delineation of the beginning and end of the stricture. In addition, it is very helpful to be able to place an ureteroscope during the procedure to visualize the stricture, which is why patients are positioned in a modified lithotomy position at NYU.

Dr. Zhao told Urology Times he considers robotic ureteral reconstruction using buccal mucosal graft to be a great option for patients with strictures due to nephrolithiasis, prior pyeloplasty, uroteroscopic injury, and trauma.

“A nice thing about the operation is that it doesn’t burn any bridges. Afterwards, patients remain candidates for other reconstruction options,” he said.

“If we think of where this procedure might fit on the ladder of reconstructive options, robotic ureteral reconstruction using buccal mucosal graft is a nice middle rung for fixing an otherwise difficult problem.”
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.

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.

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

mCRPC = metastatic castration-resistant prostate cancer; ADT = androgen-deprivation therapy.

Please see additional Important Safety Information on the next pages. Please see brief summary of full Prescribing Information on subsequent pages.
For men with mCRPC who have progressed on ADT

**ZYTIGA® & PREDNISONE:**
(ABIRATERONE ACETATE)

In the final analysis of the pivotal phase 3 trial...

ZYTIGA® + prednisone achieved a median OS of almost 3 years (34.7 months) after a median 4 years (49 months) of follow-up†

- **4.4 months improvement in median overall survival—34.7 months with ZYTIGA® + prednisone vs 30.3 months with placebo + prednisone (active compound)***
  - Co-primary end point—median OS: hazard ratio (HR)=0.81; 95% CI: 0.70, 0.93; \( P=0.0033 \)
  - Co-primary end point—at the prespecified rPFS analysis, median not reached for ZYTIGA® + prednisone vs a median of 8.28 months for placebo + prednisone; HR=0.425; 95% CI: 0.347, 0.522; \( P<0.0001 \)

**IMPORTANT SAFETY INFORMATION**

**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.

**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 enzymes CYP2D6 and CYP2C8. 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 a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

**Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).
**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 OS and rPFS. Select exclusion criteria included aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥2.5X ULN, liver metastases, moderate or severe pain, opiate use for cancer pain, prior ketoconazole treatment for prostate cancer, a history of adrenal gland or pituitary disorders, and visceral organ metastases.

*At a prespecified final analysis for OS, 65% (354/546) of patients treated with ZYTIGA® + prednisone compared with 71% (387/542) of patients treated with placebo + prednisone had died.

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

§ rPFS was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 [PCWG2] criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

In the ZYTIGA® + prednisone arm, 150 (28%) of patients had radiographic progression compared with 251 (46%) of patients treated with placebo + prednisone had died.


**Learn more today at:** [www.zytigahcp.com](http://www.zytigahcp.com)
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 assessed.

Use in Specific Populations
Pregnancy: Use ZYTIGA in pregnant women only if the potential benefit justifies the potential risk to the fetus. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women. Based on animal data, women who become 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]. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ZYTIGA with Prednisone (N=791)</th>
<th>Placebo with Prednisone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>4.5% 2%</td>
<td>0.7% 0.5%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10.6 8.0</td>
<td>3.8 2.8</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>55.6 75.0</td>
<td>53.0 79.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>32.1 30.2</td>
<td>18.3 21.8</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>10.0 11.0</td>
<td>2.0 2.0</td>
</tr>
</tbody>
</table>

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].

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 orchietomy. 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, hyperglycemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hyperphosphatemia, 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>
<thead>
<tr>
<th>System/Class</th>
<th>ZYTIGA with Prednisone (N=791)</th>
<th>Placebo with Prednisone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
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<td>10.6 8.0</td>
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<td>32.1 30.2</td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>10.0 11.0</td>
<td>2.0 2.0</td>
</tr>
</tbody>
</table>

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 disorder, 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 Bradycardia rhythm
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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Abiraterone (N=791)</th>
<th>Placebo (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>62.5 (0.4)</td>
<td>53.0 (0)</td>
</tr>
<tr>
<td>High AST</td>
<td>30.6 (2.1)</td>
<td>36.3 (1.5)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>28.3 (5.3)</td>
<td>19.6 (1)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>23.8 (7.2)</td>
<td>15.7 (5.8)</td>
</tr>
<tr>
<td>High ALT</td>
<td>11.1 (1.4)</td>
<td>10.4 (0.8)</td>
</tr>
<tr>
<td>High Total Bilirubin</td>
<td>6.6 (0.1)</td>
<td>4.6 (0)</td>
</tr>
</tbody>
</table>

Study 2: Metastatic CRPC Prior to Chemotherapy: Study 2 enrolled 1088 patients with metastatic CRPC who did not have 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

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ZYTIGA with Prednisone (N=542)</th>
<th>Placebo with Prednisone (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39.1 (2.2)</td>
<td>34.3 (1.7)</td>
</tr>
<tr>
<td>Edema</td>
<td>25.1 (0.4)</td>
<td>20.7 (1.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8.7 (0.6)</td>
<td>5.9 (0.2)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>30.3 (2.0)</td>
<td>25.2 (2.0)</td>
</tr>
<tr>
<td>Groin pain</td>
<td>6.6 (0.4)</td>
<td>4.1 (0.7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23.1 (0.4)</td>
<td>19.1 (0.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.6 (0.3)</td>
<td>17.8 (0.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11.1 (0.0)</td>
<td>5.0 (0.2)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>22.3 (0.2)</td>
<td>18.1 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.6 (3.9)</td>
<td>13.1 (3.0)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17.3 (0.0)</td>
<td>13.5 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.8 (2.4)</td>
<td>9.6 (0.9)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13.5 (0.2)</td>
<td>11.3 (0.0)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>13.3 (0.0)</td>
<td>9.1 (0.0)</td>
</tr>
<tr>
<td>Falls</td>
<td>5.9 (0.0)</td>
<td>3.3 (0.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12.7 (0.0)</td>
<td>8.0 (0.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10.7 (0.0)</td>
<td>8.1 (0.0)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>10.3 (1.3)</td>
<td>5.6 (0.6)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8.1 (0.0)</td>
<td>3.7 (0.0)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYTIGA (N=542)</th>
<th>Placebo (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38.2 (8.7)</td>
<td>31.7 (7.4)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>56.6 (6.5)</td>
<td>50.9 (5.2)</td>
</tr>
<tr>
<td>High ALT</td>
<td>41.9 (6.1)</td>
<td>29.1 (0.7)</td>
</tr>
<tr>
<td>High AST</td>
<td>37.3 (3.1)</td>
<td>28.7 (1.1)</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>32.8 (0.4)</td>
<td>25.0 (0.2)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17.2 (2.8)</td>
<td>10.2 (1.7)</td>
</tr>
</tbody>
</table>

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 1.5% 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 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. Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

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 enzymes CYP2D6 and CYP2C8.

In a CYP2D6 drug-drug interaction trial, the Cmax 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).

In a CYP2C8 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (a CYP2D6 inhibitor of the hepatic drug-metabolizing enzymes CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone [see Clinical Pharmacology (12.3) in full Prescribing Information].
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 dilatation) at doses ≥10 mg/kg/day, decreased fetal anogenital 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 2-fold and 7-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].

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 should 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 chewing or crushing. 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.

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Symptomatic urinary tract infection (UTI) is unlikely after office-based cystoscopy, although recent antibiotic exposure or hospitalization raise infection risk, according to a recent study.

Risk factors include recent antibiotic exposure, hospitalization, and data show post-cystoscopy urinary tract infection uncommon.

Of the 5,488 patients who were identified, 29 (0.53%) developed a symptomatic UTI within 30 days after the procedure. The authors cautioned, however, that this is not a true rate of infection as not all charts were reviewed and data did not include patients who may have presented at outside facilities.

High rate of quinolone-resistant pathogens
The most commonly isolated uropathogens were Escherichia coli (29%), Klebsiella spp. (21%), and Pseudomonas spp. (17%). Thirteen (45%) of the patients with a symptomatic UTI were found to have a quinolone-resistant pathogen, and about three-fourths of the 13 patients had received standard antibiotic prophylaxis, which consisted of a single perioperative oral dose of a fluoroquinolone antibiotic.

“The findings suggest patients had a breakthrough UTI and point to the importance of considering local antibiotic resistance patterns when choosing an antimicrobial agent for UTI prophylaxis,” Dr. Kang said.

“Our findings suggest that it may be reasonable to limit the use of antibiotic prophylaxis in patients undergoing outpatient cystoscopy by considering the risk of individual patients.”

CAROLINE LAI KANG, MD, PhD

Clinical characteristics associated with UTI were examined by performing a nested case control analysis that matched each of the UTI cases with four controls based on provider, office, diagnosis code, and procedure code. The variables analyzed included demographic characteristics, history of diabetes, current smoking status, immune suppression, external catheter/intermittent catheterization, non-GU tract instrumentation within 1 month, non-GU infection within 1 month, hospitalization within 1 month, receipt of antibiotics within 6 months, and receipt of a standard pre-cystoscopy antibiotic dose.

In addition, several of the variables were combined into composite variables to maximize statistical efficiency and power. The composite variables were host factors (immunosuppression, diabetes, current smoker), recent health care or antibiotic exposure (hospitalization within 1 month, non-GU infection within 1 month, antibiotic use within 6 months), and urinary colonization (catheter or intermittent catheterization or instrumentation of the GU tract within 1 month).

In univariate analysis, the only variables that were significantly associated with UTI were having an external catheter/intermittent catheterization, being hospitalized within the previous month, having received an antibiotic within the past 6 months, and the composite variable of recent health care or antibiotic exposure.

In multivariable logistic regression analysis, the composite variable of recent health care or antibiotic exposure was the only independent predictor. Patients with any of the characteristics encompassed within that composite variable had a 5.26-fold greater risk for having a symptomatic UTI compared with their counterparts without any recent health care or antibiotic exposure.

The findings will be published in an upcoming issue of Urology Practice.
Five key elements of a successful men’s health center

California group’s comprehensive program offers multispecialty care in a hospital setting

Edward Karpman, MD

The interest among urologists in developing a men’s health center (MHC) has been increasing over the last several years. There are several reasons behind this push. Urologists are realizing that we’ve missed a golden opportunity to be gatekeepers to men, similar to what gynecologists have become to women—their primary care doctors. While many urologists are trying to appease their referring physicians to maintain referral patterns, gynecologists have benefited from direct self-referral by patients because most women view their gynecologist as their primary care physician.

Another reason for this recent trend is that urology as a specialty is not well defined in the public’s eye. If you ask a person on the street, “What does a urologist do?,” many will answer that we are urine doctors. This lack of understanding by laypeople suggests that urology is in need of re-branding, and men’s health is the perfect term that encompasses the breadth and scope of our male-oriented practices.

Finally, due to apathy among urologists, we have lost control of some of our traditional disease states, and we need to bring these conditions back into the urologic fold. The best examples are hypogonadism and erectile dysfunction. As surgical subspecialists, we have neglected these two primarily medical conditions and allowed a variety of non-urologist physicians to develop injection and longevity clinics around the country under the auspices of a “men’s health center.” Every urologist I have spoken to about this issue is aware of these types of clinics in their city and every urologist has a devastating story to share of the standard care these clinics provide our patients.

We feel it is important to provide men a truly dedicated destination to be seen by their physicians.

In 2010, we started our hospital-affiliated men’s health centers at El Camino Hospital in Los Gatos, CA with the purpose of providing men a truly comprehensive program to deal with the diseases of aging and to address the aforementioned problems. At the time, there was a paucity of information and guidance for physicians to develop an MHC.

Over the last 5 years, we have developed a comprehensive, multispecialty, hospital-based MHC, and we believe that the following five elements are the keys to its success.

1. Dedicated physical space

An MHC program can be virtual or brick and mortar. We chose to develop the latter, as we feel it is important to provide men a truly dedicated destination to be seen by their physicians. Even though all of the physicians in our center—from primary care and key specialties—had separate successful practices, we brought them all under one roof. We did this on the hospital campus and in collaboration with the hospital.

The physical space was remodeled with a masculine decor, flat-screen TV, and male magazines. The idea was to create an atmosphere where guys felt comfortable—a “man-cave” feel. The clinical space has a separate entrance from other hospital services, yet is easily accessed from the main campus.

2. Hospital collaboration

We chose to collaborate with our hospital rather than start a center independently because an affiliation with a local hospital has many advantages when starting a men’s health program. Hospitals offer resources, marketing, networks, and legitimacy. Hospitals are viewed as altruistic organizations and are respected in their communities, bringing immediate credibility to an MHC.

Many men’s health diseases such as erectile dysfunction, Peyronie’s disease, and hypogonadism can be viewed by the public as sexual quality of life (but not “serious”) conditions. Collaborations with a hospital can add legitimacy to treating such conditions and distinguish your MHC from other stand-alone men’s health or “shot clinics” in your community.

3. Multispecialty physician network

The field of men’s health deals with diseases of aging that many men will encounter. Cardiovascular disease, urologic issues, and sleep disorders can make up the majority of problems for which men seek help as they get older. However, men will also need help from gastrointestinal, orthopedic, ophthalmologic, and psychiatric/psychological specialists, to name a few.

The breadth and scope of men’s health is so wide that it is impossible for any single specialty to master all of the needs. It is precisely for this reason that a collaborative effort is needed for a successful men’s health program. We invited all interested physicians to share space in the men’s health clinic to promote the concept of a one-stop men’s health center.

An example of how we strove to bring all of these programs under one roof is the development of a hospital-based sleep disorders program. Sleep disorders such as obstructive sleep apnea are extremely prevalent in our communities, occur more commonly in men than women, and are confounding factors in

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many conditions we treat daily, such as nocturia, hypogonadism, and sexual dysfunction. Our sleep disorders program was borne out of the frustration of sending hundreds of men for referrals to stand-alone sleep labs for testing, only to get back a confusing polysomnograph report without interpretation or follow-up and to hear patient complaints that the lab was located in a strip mall next to a fast-food restaurant.

We invited all interested physicians to share space in the men’s health clinic to promote the concept of a one-stop men’s health center.

Our response to this dilemma was to work with the hospital to build its own sleep disorders lab, recruit a board-certified sleep specialist, and have him see patients alongside us in the MHC.

4. Cutting-edge therapy
One of the main reasons that men, and any patient for that matter, come to a specialized center is to receive the most sophisticated and cutting-edge therapy available for their condition. An MHC is seen by patients as a place to get this type of care. As the leaders in urologic men’s health, urologists have the ability to offer not only the proven and tested methods for men’s conditions, but also to be the first to provide newer, more sophisticated cutting-edge treatments.

Unlike many injection clinics, we don’t give every man generic testosterone injections, but a choice of short- and long-acting injection therapy, subcutaneous pellets, and FDA-approved transdermal gels. We also don’t treat the obvious “low T,” but evaluate the patient’s bone health, sleep quality, prostate health, and sexual function.

Likewise, we don’t treat all men suffering from erectile dysfunction with intracavernosal injection therapy, but offer them a full spectrum of medical and surgical treatment options while also ascertaining their comorbid conditions, such as cardiovascular disease. Most importantly, we can deal with any complications that arise from these therapies, unlike the injection clinics we see sprouting up around us.

5. Outreach/marketing
A successful MHC needs to let its surrounding community know that it exists and is there to take care of the needs of men in the community. A marketing campaign is a good way to get the word out about the services provided. Marketing an MHC can be costly and is another reason why collaborating with a hospital can be beneficial to your success. Most hospitals have set aside budgets for marketing hospital service lines, and men’s health is no different from cardiovascular, orthopedic, or women’s health service lines when it comes to funding for marketing.

One of the unique outreach programs we started was an annual men’s health fair, which runs the day before Father’s Day every year. The fair includes booths for all of the specialists involved in the MHC, providing a great opportunity for patients to come by and inquire about the various specialties. We also invite industry to showcase the “tools” we use in our practices to diagnose and treat men’s health conditions. We do this in a festive environment with food, music, valet parking, and prizes for the attendees.

Summary
In summary, men’s health centers are here to stay because we, as urologists, understand their value, and our communities have shown a desire for specialized centers for men. As outlined and described above, five key elements have made our center successful, but other factors can play an important role as well. We feel strongly that we will see increasing interest by urologists in the future in support of men’s health programs around the country.

More on MHCs online
To view slideshows of leading men’s health centers across the country, visit www.modernmedicine.com/tag/mens-health-centers-slideshows.

For more on men’s health centers, see:
• Three key design elements for men’s health clinics (www.urologytimes.com/design)
• Urologists helping drive male-specific centers (www.urologytimes.com/male-specific)
How ICD-10 is changing how you do Dx coding

Problem being addressed is determining factor in medical decision making, not diagnosis

Q With the increasing requirements to use all the appropriate codes applicable to a given patient encounter in ICD-10, there may be many more diagnosis codes present for any given visit than we have been accustomed to seeing with ICD-9. Many EHR coding engines use the number of codes to determine the number of diagnoses/problems as a part of calculating medical decision-making levels and the final E&M codes for the visit. Is it appropriate to take credit for these “additional” diagnoses, or should the E&M code be reduced to match pre-ICD-10 levels for the visit?

A The implementation of ICD-10 has all of us reevaluating diagnosis coding. While ICD-10 is more specific in many areas, some of the concepts that are being addressed in training are actually pointing out the failures we have made with ICD-9 and attempting to have us make the necessary changes to code correctly as we transition to ICD-10. With quality and other potential factors being evaluated for reimbursement, the inclusion of comorbidities, more accurate diagnoses, and qualifiers will become a differentiating factor in payment. The sooner you get on board, the better your data will be.

With that caveat relative to quality data, you will need to be careful with how this affects your coding. Generally, the documentation guidelines list problems/diagnoses as a part of medical decision making. Our general focus and that of most auditors revolves around the active problem(s) being addressed and the corresponding diagnoses. Comorbidities are specifically listed for consideration under the table of risk for both presenting problem and as a risk to the patient due to the diagnostic test or treatment selected.

In short, for number of problems/diagnoses, you should only count a problem (new or established) that is being diagnosed or treated once, regardless of the number of diagnoses that are listed.

We have cautioned many times about relying on the E&M code calculator to determine the level of E&M code you should charge. The calculator may be suggesting the incorrect code for many different reasons. Certainly, if your calculator increases the level of medical decision making based on the number of diagnosis codes, then the level of code suggested will be incorrect. The problem(s) being addressed should be used in determining the level of medical decision making, not the number of diagnosis codes reported.

Q The more specific ICD-10 codes allow for changes to diagnoses as the patient progresses through a workup. Should these be considered new diagnoses for the purposes of billing the encounter? For example, a patient with asymptomatic microscopic hematuria (R31.2) may be found to have benign essential microscopic hematuria (R31.1) once his or her workup is completed. Is that a new diagnosis (and therefore counts more toward medical decision-making complexity) at the time of that later encounter, once the benign nature of the hematuria has been confirmed?

A No. As mentioned in the first answer above, the problem is the determining factor in medical decision making, not the diagnosis. The problem with hematuria as mentioned above is a good example in which the diagnosis code may change but the problem did not. Therefore, it would still be an established problem that is being dealt with during the second encounter.
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How to safeguard your patients’ information

Heightened awareness, employee training among steps you can take to protect against breaches

According to industry experts, nearly half of all Americans have had their sensitive health information compromised. In this installment in a series on privacy and information security concerns, I will discuss steps you can take to safeguard your patients’ personal information.

In April 2014, the FBI Cyber Division issued a private industry notification entitled “Health Care Systems and Medical Devices at Risk for Increased Cyber Intrusions for Financial Gain,” and concluded that health care organizations and medical devices are at significant risk for cyberintrusion and theft of personal information (http://bit.ly/FBIbreachreport). Among the FBI’s findings:

- The health care industry is not as prepared for cyber attacks as the financial and retail sectors.
- Virtual private networks, firewalls, routers, and especially medical devices are often compromised.
- Cyber criminals charge $50 for a stolen electronic health record on the black market versus $1 for a stolen Social Security or credit card number.
- Electronic health record theft is much harder to detect than “normal” identity theft.

In its 2015 “Industry Drill-Down Report—Healthcare,” Raytheon notes that the surge in cyber attacks on the health care industry may be driven by the value of the data: Health care records contain not only identity elements (name, date of birth, Social Security number, address, etc.) but also direct links to financial and insurance information for each patient record (http://bit.ly/Drilldown). Health care networks are often interconnected with devices and other large information systems (e.g., insurance companies), making them an attractive target. Health care organizations may lack the technical and administrative resources necessary to combat advanced malware.

According to one private study, criminal attacks are now the leading cause of data breaches in health care and may constitute a $6 billion epidemic (http://bit.ly/Breachstudy). Health care systems are high-value and poorly protected targets.

Steps you should take

What steps can a urology practice of any size take to confront this issue?

- Raise awareness of the problem with your physicians and staff. They are important custodians of valuable information, and may not appreciate their role in prevention or unintentional facilitation of a crime.
- Review your hiring practices and employee policy manuals. Criminal background checks, drug screening, and comprehensive applications are standard practice in industries that permit employee access to sensitive information. Are they part of your business?
- Conduct formal training for physicians and staff in privacy and security, including but not limited to HIPAA. Consult your malpractice carrier’s risk management division, which may offer this training for free. Any modest investment in prevention and training will pale in comparison to the cost of mitigating a recognized breach.
- Review your business insurance policy for coverage of cybercrime—specifically the acts of an insider or intruder who gains access to records containing medical information.
- Limit employees’ access to only that information required to perform their specific function.
- Perform regular audits of routine access to information systems, and “break glass” access. (Break glass is a method to access a record that has security settings that would not normally allow that user access.) Unauthorized access to personal information should be specifically addressed in your employee handbook.
- Engage a certified IT professional to assess your infrastructure, security practices, Internet service provider, and employee policies regarding the Internet.

Robert A. Dowling, MD
Dr. Dowling is vice president of medical affairs and policy for IntrinsiQ Specialty Solutions (an AmeriSourceBergen Specialty Group company), a board-certified clinical informaticist, and the former medical director of a large metropolitan urology practice. He resides in Ft. Worth, TX.

Practice Pointers

- According to the FBI Cyber Division, the health care industry is not as prepared for cyber attacks as the financial and retail sectors.
- Raise awareness of the problem of information security with physicians and staff, who may not appreciate their role in prevention or unintentional facilitation of a crime.
- Engage a certified IT professional to assess your infrastructure, security practices, Internet service provider, and employee policies regarding the Internet.
- Review and minimize the paper inputs, storage, and outputs in your practice; an example is to routinely shred any paper, no matter how insignificant it may seem.
Here are 7 ways you can reduce your 2015 tax bill

Harvesting capital gains/losses, prepaying state/local taxes are among steps to take now

Q Do you have any suggestions for year-end tax planning?

A Many physicians wait until March or April to start focusing on the previous year’s taxes and tax reduction. Unfortunately, many tax savings opportunities have to be accomplished by the end of the 2015 calendar year, not next April. Proactive planning prior to the end of the year can help reduce your tax bill, leaving you with more money to meet your financial goals.

As we approach the end of the year, the tax moves that you make—or don’t make—can have a significant impact on your 2015 tax return. Fortunately, there are plenty of tax-saving opportunities available to individual taxpayers, even if certain tax provisions are not resolved until the waning days of the year. Here are seven ways you may be able to reduce your tax bill for 2015.

Harvest capital gains or losses. Typically, you might realize capital gains or losses from sales of securities that can offset each other at year-end. The maximum tax rate on net long-term capital gains is only 15% (20% for those in the top 39.6% bracket). Conversely, capital losses offset gains plus up to $3,000 of ordinary income in 2015. Note: A 3.8% surtax on net investment income plus up to $3,000 of ordinary income in 2015.

Be cautious of the alternative minimum tax (AMT). Despite recent increases in exemption amounts for the AMT, many taxpayers are still trapped by this “stealth tax.” Generally, the AMT applies if you have an overabundance of tax preference items, especially if you reside in a high-tax state. Have a review of your AMT liability conducted to determine whether you should shift income items or deductions at year-end.

Prepay state and local income taxes. Absent other circumstances, the conventional wisdom is to reduce your current income tax bill whenever possible. Therefore, you might arrange to prepay any state and local income taxes due on Jan. 1, 2016 before the end of the year. As a result, you can increase your deduction for state and local taxes in 2015.

Combine all elective medical expenses. For 2015, the threshold for deducting medical expenses for most taxpayers is 10% of adjusted gross income (AGI), although it is 7.5% of AGI for those age 65 or older. If you have a chance at a deduction for 2015, try to move elective expenses, such as physical examinations, to this year. Otherwise, you might as well postpone those expenses until next year.

Split income with family members. When appropriate, transfer income-producing property to low-income-tax-bracket family members, who may benefit from a 0% rate on long-term capital gains.

One advantage of creating a private foundation is being able to decide which charities to make distributions to while still retaining control of the assets.

Financial Tips

- Many tax savings opportunities have to be accomplished by the end of the 2015 calendar year, not next April.
- Prepaying any state and local income taxes due on Jan. 1, 2016 before the end of the year allows you to increase your deduction for state and local taxes in 2015.
- When appropriate, transfer income-producing property to low-income-tax-bracket family members, who may benefit from a 0% rate on long-term capital gains.
- One advantage of creating a private foundation is being able to decide which charities to make distributions to while still retaining control of the assets.

Make charitable contributions. Generally, you deduct the full amount of cash or cash-equivalent gifts made to qualified charities, assuming you keep the proper records. Also, you may deduct the fair market value of gifts of appreciated property if certain requirements are met. However, special limits often apply, including a possible reduction in deductions for certain high-income taxpayers.

If you have a chance at a deduction for 2015, try to move elective expenses, such as physical examinations, to this year.

Lock in education tax breaks. If you are sending a child to college, you may be able to claim either one of two higher education credits, subject to phase-outs at certain income levels. Previously, you also had an option of a tuition deduction, subject to a phase-out, but this tax break technically expired after 2014 and is currently in limbo. In any event, pay qualified expenses in 2015 to maximize any available tax break.

Depending on your situation, one or more of these strategies may make sense for you. Be sure to consult with your tax adviser prior to the end of the year to determine whether there are any proactive tax strategies that you can implement for your own specific benefit.

Q What are the advantages of creating a private foundation?

A With this strategy, you make contributions to a foundation and get a charitable tax deduction just as you would with any qualified charitable organization. Then, as the director, you get to decide which charities you want to make distributions to while still retaining control of the assets. Other advantages include reduced future estate and income taxes since you no longer own the contributed property. In addition, after your death, your children and grandchildren can take over as directors of the foundation.

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.

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.
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The time has arrived for all urologists to become involved in the business side of their practice. It doesn’t matter the size or shape of the urologist, size of the practice, location of the practice, or employment status of the urologist; we all need to have an interest in the business aspects of our practices.

It wasn’t but a few decades ago that urologists had small patient volumes and large profit margins. The tide has changed in the new millennium, and now we see large volumes of patients with razor-thin profit margins. That, compounded by rising overhead costs, translates to an erosion of our bottom line. Therefore, it behooves us to become involved in the business of our practice.

Many urologists believe that the economics of health care means monitoring accounts receivable, relative value units, and reducing overhead expenses. In this first installment of a two-part article, I will discuss other business aspects that are imperative to every successful urology practice.

Be a leader
Moving forward, we will need core competencies not taught in medical school. All of us know how to diagnosis and treat urologic conditions. But do we know how to manage other physicians and staff? Leadership requires setting the example; ie, being an on-time physician and learning the art of delegating to others. Urologists should only do what can’t be done by anyone else in the practice. All else should be delegated. A medical school education is not necessary to ask about surgical history and how many cigarettes or alcoholic drinks a patient consumes.

Patient/customer satisfaction
The word “customer” is not a dirty word and should be part of our medical lexicon. Doctors and staff must go out of their way to ensure that every patient has a positive experience at each and every interaction with the doctor and the practice. This includes the first telephone interaction between a new patient and your receptionist. A potential patient put on hold or directed through a complicated phone tree for 20-30 minutes before speaking to a human will often hang up and go elsewhere for his urologic care.

Measuring patient satisfaction is good for business. Patient satisfaction scores are going to be used as part of the reimbursement formula for physicians. Those who have higher scores are going to receive more compensation than those with lower scores.

Manage your reputation
What is the physician’s most precious possession? Patients, some might answer. Others might say education and training. But the real answer is the physician’s reputation. Doctors live and die by their reputations. These reputations take years to build but are so fragile that they can crumble in a matter of seconds.

Urologists should only do what can’t be done by anyone else in the practice. All else should be delegated.

This is largely because in today’s digital age, where news is instant thanks to social media, blogs, and search engines, your practice’s reputation can take a turn for the worse almost instantly. What can you do to protect yourself?

At a minimum, physicians should monitor their practice reputation by conducting periodic searches—“Googling” their name—to identify what information about their practice is already visible online. You may find that three, four, or even 10 reviews are already posted on various review sites online. Don’t be surprised if one or two are negative.

Do not let one disgruntled patient ruin your reputation. Take an active role and generate positive reviews to drown out any negative remarks made by an occasional patient. Protecting your valuable reputation is important for the business of your practice.

Be transparent
Our patients demand the same high-quality service they would expect from any other service provider, including urologists. Therefore, we need to make our services more transparent.

It’s no surprise that access to information about the price and quality of health care services can help patients/customers make better decisions about their care. What is surprising is how difficult it has been for patients to get this information. The truth is that patients rarely know the real cost of care until after they’ve received it. And the price—and quality—of a particular service can vary considerably by provider. What’s more, higher price does not necessarily equate with higher quality.

Today, patients/customers faced with high-deductible health plans and increasing out-of-pocket expenses demand quality and cost information. They seek answers to questions such as:
- What will my true out-of-pocket costs be?
- Where can I get the best care for my money?
- What if I can’t pay?
- If my doctor ordered this test or drug, does my insurance cover it? If the answer is no, why not?

It is good business to give patients a reasonable estimate for the cost of care.

Consider wellness as well as illness
It will be good business to think about moving from “sick care” to “well care.” As physicians, we were trained to treat medical problems and conditions. Today, the public is very interested in staying well, and it is going to be good for our business to focus on wellness as well as illness. Examples include teaching young men about testicular self exam, discussions on kidney stone prevention, the role of diet in various urologic diseases such as prostate cancer, and motivating patients to participate in smoking cessation programs, as this wellness behavior may improve their erections.

Hopefully, you can appreciate now just how many business variables are in play in today’s urology practice. As health care continues to change and evolve, your survival will depend on changing and evolving with it. In the next installment, I will provide suggestions on improving not only your business but also the quality of your care.
The UroLift® System is a unique minimally invasive alternative to major surgery for the treatment of BPH. UroLift permanent implants are individually tailored during delivery to transprostatically reshape the prostate, thus reducing urethral obstruction directly without ablating, cutting or removing prostate tissue. The procedure may be done in an outpatient setting and often local anesthesia is used.1

- Immediate, visible result1
- Rapid symptom relief2
- Preservation of sexual function3
- Typically no catheter required after treatment1

Clinical data shows patients receiving UroLift implants report rapid symptomatic improvement, improved urinary flow rates, and sustained sexual function. Patients also experience a significant improvement in quality of life.1

Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

**IMPROVE YOUR BPH GAME TODAY** Check out the data and learn more at UroLift.com
Q: How did you become involved with stone disease?
A: I have a PhD in mechanical engineering, and I’ve studied sound. I’ve always had an interest in medical ultrasound. I’m on the Executive Council of the Acoustical Society of America, and I served on the American Institute of Ultrasound in Medicine’s Bioeffects Committee.

As someone interested in sound, I think shock wave lithotripsy is an amazing technology for breaking kidney stones. About 25 years ago, when lithotripsy was still new, I became involved with Dr. James Lingeman’s research group, studying who lithotripsy was most effective with and what its safety limits were. That research program, which was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, was a collaboration among clinicians, basic science anatomists, and biologists at Indiana University as well as shock wave physicists at the California Institute of Technology and engineers from the University of Washington who knew ultrasound and acoustics.

Q: Please describe how you’re using ultrasound to propel and break up stones.
A: We have two new technologies we’re developing, and they come out of the 20 years of lithotripsy research we’ve done.

With the first technology—ultrasonic propulsion—the user places the handheld probe against the patient’s skin, and the probe emits an ultrasound wave to reposition stones and to create real-time ultrasound imaging to target and obverse stone movement. When the user touches the screen in the location of the stone, in between imaging pulses, a longer duration push pulse is focused on the stone. The push pulse reflects from and imparts momentum into the stone, which makes the stone hop. We want to use this technology to expel small stones and fragments from the kidney to avoid surgery, to dislodge larger stones from an obstructing position in the ureteropelvic junction or possibly ureterovesical junction to relieve pain and avoid urgent surgery, and to improve access in a procedure like percutaneous nephrolithotomy.

With the second technology—burst wave lithotripsy (BWL)—broadly focused ultrasound is used to crumble stones into uniform small fragments. We took lessons we’ve learned from lithotripsy that enabled us to make a different device that pulverizes even the hardest stones quickly and completely in preliminary experiments. We use a broad beam width and longer duration pulse. We try to minimize cavitation in the tissue and limit cavitation to the surface of the stone. Even the hardest stones seem to be breaking.

Q: That’s really fascinating and in many ways potentially groundbreaking. How safe is this technology? How do you know that?
A: The stone-breaking technology, BWL, is not as far along in development, but it utilizes low pressure—about 5 to 10 MPa—compared to lithotripters, which operate at 50 to 100 MPa. We have done limited animal studies, and we feel we have a safe range where we can break stones and not cause injury. We also have ultrasound feedback that allows us to see when cavitation that may cause injury occurs in the tissue. When cavitation is detected, the output is turned off, allowing cavitation to dissipate before resuming.

With ultrasonic propulsion, we have completed a clinical trial with 15 subjects and that manuscript is in press in the Journal of Urology. There were no adverse events associated with the treatment. It’s basically a diagnostic probe with diagnostic ultrasound output levels. So I think you would appreciate that it would probably be safe. It was performed in patients who were awake. They did not experience pain. There were two patients who felt some sensation in the kidney, but did not require stopping the procedure.

Q: That’s great. Who should be performing these procedures?
A: Our primary “target audience” is urologists, who have been supportive of this technology from the beginning. This has grown out of urology research supported by the AUA and NIH/National Institute of Diabetes and Digestive and Kidney Diseases. We even have NASA funding because stones are a concern in space.

We do think it is urologists who are going to be responsible for the movement of the stones for any obstructions that could occur. In addition, though, if its effectiveness is established, there could be applications in the emergency department; emergency medicine physicians might use the technology to dislodge a large stone obstructing the ureteropelvic junction retrograde into the kidney to relieve pain and avoid the need for urgent intervention. The urologists would then schedule any necessary intervention for the stone and potentially use either of these new technologies.

Q: Of the potential uses for this technology, which do you think will have the greatest impact, and why?
A: I tend to follow what urologists tell me. For ultrasonic propulsion, I think interest is split almost equally between moving a large stone to relieve symptoms of obstruction and delay intervention and expelling small de novo stones or small fragments that might remain after lithotripsy to avoid additional intervention. We have also heard a list of other uses in which urologists are interested, such as accessing stones during surgery or facilitating lithotripsy in various ways.
We spun off a company out of the University of Washington called SonoMotion. I think the company will probably first focus on expelling fragments. Personally, I hope this comes to be seen like a toothbrush; you do this every so often and clean people out before they need surgery.

Q: What are the limitations of this technology?
A: It’s still early, so we’ll learn more about limitations. BWL in particular is in the early stages, but a lot of our effort is on feedback for when the stone is fully comminuted. For ultrasonic propulsion, we learned a great deal in the clinical trial. We learned we wanted to move more stone material more quickly. I don’t think we appreciated how much debris might be left after lithotripsy. We built a system originally to steer one stone through a maze. In the trial, we saw we just needed to move more stone mass in the right direction and then the kidney could take it from there.

We had patients get off the table and pass stones immediately. Our post-lithotripsy patients passed over 30 fragments among them. There was a lot of small (about 2-mm) material that we were getting them to pass.

In terms of limitations for ultrasonic propulsion, although urologists are well trained in ultrasound, they’re still not as familiar with it as computed tomography. The biggest challenge is aligning the direction of push with a path where the stone can travel. Finding the correct acoustic window can be challenging, as you have to work around the ribs. However, the lower pole is a pretty nice target because it’s below the ribs and you’re pushing in a favorable direction.

Q: What’s next for this technology?
A: For ultrasonic propulsion, we have been approved by the FDA for another 15 subjects at our institution. Our research group clearly learned a lot; we have safety headroom and we have clear steps we can take to improve the system based on what we learned. That gave us the confidence to let the university spin off the technology to SonoMotion Inc. We hope that will enable us to move quickly to get this in the hands of more users and obtain more feedback on exactly where ultrasonic propulsion fits best in the management of stones. We hope this will take off commercially, so it can be used to help patients.

In addition, we’re continuing to work on breaking stones, and we hope that in a couple of years BWL moves into a clinical trial so we can test if we have a better way of breaking stones.

At UPMC, our physician and researcher teams are working to better understand the mechanisms of prostate carcinogenesis and progression by studying major pathways, such as androgen receptor signaling, and developing new, targeted small molecule therapeutics. In addition, we are defining prostate cancer from a genomic perspective, and have discovered novel genomic abnormalities and genetic fusions associated with disease recurrence. Our ultimate goal is to find new prostate cancer treatments directed at those who require treatment to improve survival and quality of life. To learn more, visit UPMCPhysicianResources.com/Urology.
PRIVATE V. EMPLOYED  
continued from page 1

records (EMRs), meaningful use, value-modifier systems, and more.

The employment relationship lasted 3 years and 10 months. He has since re-established his former urology group. While Dr. Fabrizio can’t talk personally about his experiences, he offers a broad view of the differences between being in a hospital-based and private practice.

Administrative responsibilities

Lesson 1: Hospital employment removes some administrative burdens, but there are drawbacks in giving them up.

Dr. Jumper has multiple administrative duties as a hospital employee. These include responsibilities as academic faculty, as director of pediatric urology, and as chair of the systemwide Clinical Safety and Outcomes Committee. However, unlike his peers in private practice, Dr. Jumper wasn’t responsible for designing, purchasing, and educating staff to use the EMR. The hospital did that. And Maine Health helps the urologists in measuring and monitoring outcomes.

“As an employed urologist, it’s less on your shoulders because it’s the responsibility of the entire hospital system to come up with monitoring and requirements to get the data. If we were in private practice, we would have to figure all of that out on our own computers,” he said.

It’s not all smooth sailing, however.

“Although the hospital paid for all of the costs associated with the EMR, including EMR-associated expenses, often are not subject to RVU [relative value unit] requirements,” Dr. Jumper said.

Lesson 2: A decrease in administrative duties may not mean a decrease in cost.

Dr. Fabrizio said some of the typical administrative headaches urologists face in private practice are alleviated when they become employed.

“You don’t have to worry about benefits, human resources, compliance issues—those types of things—because they’re done on a central basis,” he said. “And you do get incorporated into the electronic medical record, so that’s done for you at the practice level. But the costs that are attributed to the EMR are also assigned to you at the practice level in many ways.”

Take-home: Typical administrative burdens, including practice-related human resource and compliance issues, are taken off the employed urologists’ shoulders. But there’s no free lunch. Costs assigned to practice administration, including EMR-associated expenses, often are part of contract negotiations.

Autonomy

Lesson 3: “Losing my autonomy was the most difficult thing to swallow,” Dr. Jumper said.

The process, or red tape, in a hospital system can result in even small practice changes taking a year or more, or not happening at all, according to Dr. Jumper.

Lesson 4: Health systems’ and specialty practices’ strategies don’t always mesh.

“You do lose some autonomy when you go into a health system,” Dr. Fabrizio said. “When you lose autonomy, unless your contract allows you to specifically do so, you lose control of the ability to add staff or maybe even expand certain business lines because of cost constraints.

“Health systems and specialty surgical practices often have misaligned strategies. Health systems are typically focused on cost constraints, and that may limit your ability to grow.”

Take-home: Urologists transitioning or going into hospital employment have to relinquish their ability to make many decisions about practice hiring, expansion, spending, and more.

Reimbursement/income

Lesson 5: When negotiating contracts with hospital systems, consider ways to hedge against economic downturns.

There are advantages to hospital employment when it comes to reimbursement, according to Dr. Jumper.

“Certainly, in our neck of the woods, we could not be making this kind of money in private practice because the hospital gets more money for what we do. We make money for them, and they can guarantee us more money,” Dr. Jumper said.

While a part of Dr. Jumper’s income is guaranteed, some of his pay is tied to meeting predetermined RVU production quotas. His contract stipulates that if he exceeds the quota, he gets a bonus. But if Dr. Jumper doesn’t meet the goal, he risks losing a portion of his pay.

The problem is, production isn’t always in urologists’ control.

Dr. Jumper didn’t meet RVU quota for the year last year, he said, because of factors that were not related to performance. The hospital decided not to diminish his pay, because, Dr. Jumper said, he has a good relationship with hospital administrators.

“They realize everything else that I’m doing, including the quality metrics, [matters more]. And they realized the fact that we took on a new pediatric urologist, which siphoned off some of my referral base. They can also understand that I have a 17% no-show rate. We live in a rural state, with a large number of Medicaid patients,” he said.

On the income front, Dr. Jumper recommends urologists negotiating contracts with hospital systems find ways to hedge against economic dips and reimbursement challenges. Dr. Jumper, who started contract negotiations with Maine Health in 2008, in the middle of the Great Recession, said his group built a 2.5% annual pay increase into its 5-year contract.
Lesson 6: Reimbursement may increase, but so may expenses.

Typically, everything the urologist does in a health system is two- to threefold more expensive than in private practice, according to Dr. Fabrizio.

“Health systems enjoy a significant reimbursement pop for services provided. Likewise, expenses are higher in health systems. So, you become part of that equation,” Dr. Fabrizio said. “While reimbursements go up, expenses go up. And if your contract is tied to either of those, on the expense side of the equation, you could be adversely affected.”

Health systems cannot reimburse urologists based on the actual revenue they bring into the health system, Dr. Fabrizio said. “You may bring two-, three-, or fourfold the revenue now that you’re a hospital employee, but you don’t get to share in that service line revenue stream,” he said. “In general, health systems have trouble recognizing that service line revenue stream, meaning all the ancillaries you bring into the health system. Contracts have to be ‘fair market’ valued. So, there is some misalignment in the strategies contractually between the private group and the health system.”

And health systems might be basing proposed urologist salaries on benchmarks that aren’t in urologists’ favor. Hospital contracts typically are based on market analysis or fair market valuations, according to Dr. Fabrizio. But fair market is a very broad term that’s defined as the benchmark they utilize for full-time equivalents and support staff. Urologists’ salaries can be affected, depending on the benchmarks a health system uses, he said.

Urologists should also keep in mind that while salaries might be higher in health systems, job security after the contract ends is up in the air. And starting a private practice after a few years in a hospital setting is no easy task, according to Dr. Fabrizio.

Take-homes.

“Health systems are typically focused on cost constraints, and that may limit your ability to grow.”

MICHAEL FABRIZIO, MD

Remember, the national benchmarks hospitals use might not be the benchmarks urologists should use when conducting negotiations with hospitals. “You don’t realize how valuable you are until push comes to shove. And the hospital is not going to give you that data,” Dr. Jumper said. “You should realize that urology is the number one user of pathology services in all hospital systems.”

Finally, employed urologists should try to be a good citizen and build relationships with their employers. Those relationships could come in handy when contractual issues affecting pay come up.

Practice growth/recruitment

Lesson 7: Recruiting new physicians can be nearly impossible in private practice.

It’s much easier to recruit nurses, nonphysician providers, and urologists in a hospital.

Please see PRIVATE V. EMPLOYED, on page 28.
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based employment structure, according to Dr. Jumper.

“The hospital can offer better money and better benefits than a private practice,” he said. In fact, recruitment was one of the big reasons Dr. Jumper left private practice in Maine. Urologists coming out of residency are demanding salaries that rival their more experienced peers, he said. Yet, it takes new doctors about 2 to 3 years to generate a profit. That’s hard for a private practice to absorb, unless it’s a large, established group, according to Dr. Jumper.

Lesson 8: Hiring is out of your control in a health system.

While recruiting might be easier in a health system, the growth of a department and ability to hire is out of many employed urologists’ control, according to Dr. Fabrizio.

“A potential problem with a health system is they may see your particular service line as not being a priority for the system. Certainly, your practice is your priority,” Dr. Fabrizio said. “But quality of life could deteriorate if you’re not allowed to make decisions, according to Dr. Jumper. “With your own practice, you can always control your own destiny.”

Take-homes. Recruiting urologists and non-physician providers often is easier in a health system than it is in a private practice—unless that practice is large enough to absorb expenses related to the time it takes to get a provider’s production up to par. Expanding service lines and hiring preferences are not as easy in a health system as in a private practice because urologists tend not to be the decision makers.

Quality of life

Lesson 9: Quality of life at a hospital is different than it is in private practice—not better or worse.

“I actually enjoyed it 10 years ago when I saw twice as many patients as I do now. And I had a stenographer that would type up all the reports at the end of the day, and I made 20% to 30% less than I do now. It was satisfying,” Dr. Jumper said.

Now, he’s a spoke in a wheel. He sees fewer patients but has more deskwork. For example, he has to type his EMR reports, and, by his own admission, he’s not a good typist. He offered to pay out of pocket for an assistant to type the reports, but was told he couldn’t because then everybody would want to do it. That, he said, goes back to the loss of autonomy.

“Of course, with the residency program, I spend more time teaching. On another level, I can take pride in producing urologists,” Dr. Jumper said. “So, it’s a tradeoff. It’s a totally different mindset.”

Lesson 10: Quality of life doesn’t necessarily change in the transition from one type of practice to another.

“You still have your call responsibilities,” Dr. Fabrizio said. “But quality of life could deteriorate if you’re not allowed to make decisions, if you want to expand the service line, or get more FTEs for your office. It goes both ways.”

Take-homes. There are quality of life tradeoffs in both working situations. Urologists who enjoy seeing patients and the relationships they’ve built with their patients might not get as much satisfaction as employed physicians. On the other hand, employed physicians might find such things as having less responsibility for practice administration to be a quality of life boost.

Patient impact

Lesson 11: Employment improves patient access but that access comes at a price.

Since the hospital has been able to recruit more urologists, patients who used to wait 6 months to see Dr. Jumper in private practice have much shorter wait times.

“The downside is, everything costs more because we’re part of a hospital. The private practice does not get paid as much as the hospital for the same services,” he said.

Lesson 12: You stand to lose long-time patients if you join a health system from private practice.

In a closed health system, for example, if referring doctors aren’t part of the system, chances are urologists who used to get the doctors’ referrals won’t continue to see those patients, according to Dr. Fabrizio.

Another roadblock for patients seeing urologists and others employed by health systems is the increased cost.

“What most health systems are doing around the country is something called provider-based billing for Medicare patients,” Dr. Fabrizio said. “So, I’ve been seeing Mr. Smith for 20 years in my practice, and I’ve been billing a professional fee for Mr. Smith’s annual office visit. Now, Medicare patients get two bills when physicians join a health system. They get a bill to see the doctor but then they also get a facility fee, and that facility fee is between $150 and $200. If Medicare patients don’t have secondary insurance, they are responsible for a 20% deductible for that facility fee.”

Take-homes. While a hospital’s ability to recruit urologists and non-physician providers might increase patient access to the specialty, patients’ wallets take a hit when urologists join hospital systems.

In the end, these are generalizations. The decision about whether to become employed or have a private practice is not one to base on a single issue. Other factors often come into play, such as the urologist’s local market and how much power hospitals have in any given community, Dr. Jumper said.

UT Figure

REASONS FOR CONSIDERING HOSPITAL EMPLOYMENT

68% Less administrative hassle
38% Better reimbursement
34% More free time
23% Job security
12% Other

Source: Urology Times 2014 State of the Specialty survey

HOW INDEPENDENT DOCS CAN STAY THAT WAY

Across the country, hospitals are buying up independent practices left and right. For many reasons, the notion of being employed is becoming a tempting possibility for practitioners. However, consolidation has also raised questions of higher health care costs, compromised quality of care, and a loss of physician autonomy.

In a podcast from Urology Times sister brand Physicians Practice, Marni Jameson, executive director of the Association of Independent Doctors, joins Physicians Practice Managing Editor Gabriel Perna to talk about this trend. Jameson recently spoke on this topic at the Medical Group Management Association annual conference in Nashville, TN. To listen to the podcast, visit: http://bit.ly/jamesonpodcast.
Speak Out
What would you like to change about how you practice urology?

“The thing I would love to change would be being able to not worry as much about processes and just take care of the patient, to do medicine, and not worry about all the pre-authorization and all the time we have to spend getting patients through the system. You have to spend a lot of time filling out pre-authorization; it’s a lot of paperwork. I have a wonderful nurse who does what she can, but the doctor really has to put in the effort to make a good argument if we want to get approval for our patients, and even then there’s no guarantee.

The other issue is juggling everyone’s insurance. You have to try five different drugs before you can get permission to use the one you want. I think most physicians use drugs appropriately, generic and otherwise.”

Nina Davis, MD
Portland, OR

“What has changed so drastically is having to deal with electronic medical records. It tends to be somewhat cumbersome, time-consuming, and aggravating. It... has prompted the use of more physician extenders and scribes. Unfortunately, this detracts from the physician-patient dialogue and the attempt to focus on providing personal and quality patient care to what we now refer to ourselves as a ‘data entry’ person trying to practice medicine at the same time.

There’s no doubt about the fact that EHRs can also be helpful, especially for extracting data. It also allows us to quickly list patients with certain urologic issues.

‘It’s a necessary evil,’ is here to stay, and has certainly changed the way we practice. I just wish there was a better way.”

William Bogache, MD
Myrtle Beach, SC

“I think it would be to restore the focus back on the patient/physician relationship and get rid of all of the other distractors — insurances and the financial part — everything that gets in between a patient... and the physician. That simple relationship has become so much more complicated with the current health care environment. Health care should be a contract between the physician and the patient. More physician-directed delivery of health care would be a step toward restoring that relationship. For that to happen, we would have to be the ones driving that and right now it doesn’t seem like physicians are the ones who are organized or empowered or feel like they’re in the position to make that kind of change, and one physician at a time can only do so much. It will take groups of people coming together to make that change.”

Tamra Lewis, MD
Lake Barrington, IL

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SonaCare Medical receives FDA clearance for HIFU prostate device

Charlotte, NC—SonaCare Medical, LLC received FDA clearance to market the Sonablate 450 in the U.S. for the ablation of prostate tissue. Sonablate uses high-intensity ultrasound (HIFU) to deliver precise and focused ablation, according to SonaCare Medical. It’s powered by A3 Technology, which allows physicians to aim energy at specific tissue using integrated ultrasound imaging and sophisticated planning tools; ablate targeted tissue with HIFU ablation that provides pinpoint accuracy while sparing untargeted tissue; and analyze procedure results using real-time ultrasound imaging along with advanced tissue change monitoring software. SonaCare Medical was expected to begin U.S. distribution in October.

For more information, visit www.SonaCareMedical.com.

FDA approves expanded use of trial system for incontinence therapy

Dublin, Ireland—The FDA has approved the use of the Verify Evaluation System for basic evaluations, which last 3-7 days, thereby expediting the potential for long-term restoration of bladder or bowel function. The Verify System allows patients to test the benefits of Medtronic Bladder or Bowel Control Therapy (sacral neuromodulation), delivered by the InterStim System for the chronic symptoms of overactive bladder, nonobstructive urinary retention, or bowel incontinence in patients who did not have success with more conservative therapies. The Verify System includes a wireless touch-screen controller and a small, concealable external neurostimulator device. It allows patients to perform many normal daily activities while undergoing the evaluation. A trial can be considered a success if a patient experiences a significant reduction in bladder control symptoms.

For more information, visit www.medtronic.com.

Small-size catheter for men is compact, portable, discreet

Minneapolis—Coloplast announced the U.S. launch of SpeediCath Compact Male, a compact catheter for men. The new product is less than half the size of a standard male catheter and may be stored, carried, used, and disposed of discreetly. The SpeediCath Compact Male all-in-one design is instantly ready to use, featuring “no touch” insertion and withdrawal that provides a level of convenience and is usable in any location at any time, according to Coloplast.

For more information, visit www.coloplast.us/.

Wearable technology offers solution for continence care, management

Sydney, Australia and Atlanta—The Smart Incontinence Management (SIM) medical device is the world’s first wearable integrated digital technology solution for continence care assessment and management, according to Simavita. It detects multiple incontinence episodes through a sensor embedded into an adult incontinence pad. The SIM sensor is a single-use disposable device that connects to a durable transceiver that records and wirelessly transmits incontinence data to a server for storage and processing. Collected data are synchronized with incontinence-related observations recorded by staff via an application displayed on a tablet or phone and can be used by the clinician to develop an evidence-based toileting plan.

For more information, visit www.simavita.com.

System helps safeguard scopes’ working channel from damage

El Segundo, CA—KARL STORZ Endoscopy-America, Inc. announced the availability of the FLEX-GUARD Laser Fiber and Sheath System, which helps to safeguard ureteroscopes’ working channel from both mechanical and thermal damage. The system is used with the company’s FLEX-XC or FLEX-X2 flexible ureteroscopes. The FLEX-GUARD comes pre-assembled with a ScopeSafe laser fiber and protective sheath. The easy-to-use sheath with Micro Adjuster have clear markers to indicate when the sheath is covering the fiber tip and is ready for insertion, according to KARL STORZ. This design facilitates multiple passes of the fiber through a deflected scope, simplifying the procedure. The FLEX-GUARD is available in three sizes, and non-sheathed ScopeSafe laser fibers are also available.

For more information, visit www.karlstorz.com.

To have information on your company’s product or service published in this section, send news releases and photos to: UT@advanstar.com
Publication is subject to space availability.
Advanced RCC agent granted breakthrough therapy designation

The FDA has granted breakthrough therapy designation to nivolumab (Opdivo) for the potential indication of advanced or metastatic renal cell carcinoma (RCC). The designation is based on results of CheckMate –025, a phase III study that evaluated the survival of patients with previously treated advanced or metastatic clear-cell RCC versus everolimus (Afinitor). The trial was stopped early in July 2015 because an assessment conducted by the independent Data Monitoring Committee concluded that the study met its primary endpoint of overall survival, demonstrating superior overall survival in patients receiving nivolumab compared to the control arm. Manufacturer Bristol-Myers Squibb presented further data from this study at the European Cancer Congress in Vienna, Austria.

IDE approval granted for implantable neurostimulator

StimGuard recently announced that it has received FDA Investigational Device Exemption approval to launch a clinical trial of its percutaneously implantable device for the treatment of urgency urinary incontinence resulting from refractory overactive bladder (OAB) syndrome. The clinical trial will focus on implanting a small neurostimulator at the tibial nerve under ultrasound and utilizing a discreetly worn external transmitter to provide energy and therapy to the implanted device, according to StimGuard. The trial will assess the effectiveness of delivering pulsed electrical energy to surrounding tibial nerves that travel to the sacral nerves to regulate bladder function.

Lancet data: Thyroid Ca Tx may have benefit in metastatic RCC

Results from an investigational phase II clinical trial evaluating lenvatinib in combination with everolimus (Afinitor) and lenvatinib and everolimus alone for the treatment of metastatic renal cell carcinoma (mRCC) were recently published online ahead of print in The Lancet Oncology (Oct. 15, 2015). The randomized, open-label, multicenter trial evaluated progression-free survival in patients treated with the combination (n=51), patients who received everolimus alone (n=50), and patients treated with lenvatinib monotherapy (n=52). Based on the results of the study, the FDA granted lenvatinib breakthrough therapy designation for patients with advanced or metastatic RCC who were previously treated with a vascular endothelial growth factor-targeted therapy. Lenvatinib is currently available as LENVIMA for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

Companies enter agreement for phase II trial of prostate Ca vaccine

Generex Biotechnology Corporation’s immunotheapeutics subsidiary, Antigen Express, Inc. has entered into a memorandum of understanding with CompanDX Ltd. to conduct a phase II clinical trial of the Antigen Express proprietary prostate cancer vaccine AE37. Under the terms of the agreement, milestone payments and royalties will be paid to Antigen Express in exchange for the rights to AE37 for the treatment of prostate cancer.

Studies demonstrate infertility diagnostic tool’s clinical utility

Aytu BioScience, Inc. recently presented clinical data from two prospective clinical studies of its MiOXSYS System that demonstrated its clinical utility as a tool for measuring oxidation-reduction potential to assess the degree of oxidative stress levels in human semen, which is broadly implicated as a major cause of male infertility. The results were presented at the American Society for Reproductive Medicine annual meeting in Baltimore.

Phase II trial of bladder Ca agent reaches target patient enrollment

Borealis-2, an investigator-sponsored, randomized phase II bladder cancer trial, has met its target enrollment of 200 patients, reported Oncogex Pharmaceuticals, Inc. Designed to evaluate apatorsen in combination with docetaxel (Taxotere) in patients with advanced or metastatic bladder cancer who have disease progression following first-line platinum-based chemotherapy, Borealis-2 is sponsored by Hoosier Oncology Group and is being conducted at 27 sites across the United States. Apatorsen (OGX-427) is designed to inhibit production of heat shock protein 27, disable cancer cells’ defenses, and overcome treatment resistance.
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Radiation centers face steep payment cuts

ASTRO: Proposed reductions would close 30% of RT centers

Washington—Proposed cuts by the Centers for Medicare & Medicaid Services (CMS) in Medicare payments for radiation oncology services would force an estimated 30% of community-based radiation therapy centers to close their doors, according to a statement sent to CMS by the American Society of Radiation Oncology (ASTRO).

In the statement, ASTRO Chief Executive Officer Laura I. Thevenot took issue with proposed payment revisions that would slash radiation oncology payments by 5%-7%, and possibly higher, depending upon the clinic’s patient population.

Cuts would have ‘detrimental effect’

“The proposed cuts follow on cuts of more than 20% to freestanding centers over the last 6 years,” ASTRO said. “The additional impact of both the equipment utilization rate assumption change and the removal of direct practice expense inputs for image guidance would have a detrimental effect on the ability of many freestanding practices to remain viable. This could limit access to care for cancer patients, particularly in rural and medically underserved areas.”

In addition to those practices that told ASTRO in a survey that they may have to close, 62% said they might have to consolidate practice locations and about 41% were concerned they would have to stop accepting Medicare patients.

“The proposed cuts are too deep and too fast for many freestanding oncology centers to absorb,” Thevenot said. “We urge CMS to work with radiation oncology stakeholders to protect access to radiation therapy services by significantly limiting these proposed cuts and reconsidering several proposed policies.”

Laura I. Thevenot
ASTRO Chief Executive Officer

“We urge CMS to work with radiation oncology stakeholders to protect access to radiation therapy services by significantly limiting these proposed cuts and reconsidering several proposed policies.”

“By delivering top notch care close to home, community cancer clinics are an essential part of our healthcare system,” Tonko said. “By asking CMS to reevaluate these flawed cuts that could harm patients with a diagnosis of breast or prostate cancer, we can ensure that community cancer clinics will be open for those in need.”

Interoperability becoming serious problem

Meanwhile, in another development involving cancer care, the American Society of Clinical Oncology (ASCO) held a congressional briefing in September on Capitol Hill to inform lawmakers and key staff members about how the lack of interoperability in health information technology (HIT) is becoming a serious problem.

During the briefing, ASCO outlined steps Congress should take to advance the widespread interoperability of electronic health records (EHR) and prevent “information blocking,” which artificially limits efficient sharing of information between medical practitioners.

ASCO pointed out in a position statement issued during the briefing that the Office of the National Coordinator for Health Information Technology defines an interoperable HIT system as one that “makes the right data available to the right people at the right time across products and organizations in a way that can be meaningfully used by recipients.”

To meet this standard, ASCO said, all HIT initiatives must be able to electronically share clinical information between practitioners.

“The treatment of cancer is complex, often requiring coordination of care and the exchange of detailed clinical information among multiple health care providers using different health information systems,” observed ASCO President Julie M. Vose, MD. “Widespread interoperability for sharing electronic health information is not just a matter of efficiency, but critical for optimal cancer care.”

ASCO pointed out that EHRs often contain data that cannot easily be shared among physicians or contributed to quality improvements, public health reporting, or analytics. In addition, ASCO said it is observing a growing trend in commercial business practices that are creating barriers to interoperability, including information blocking—the practice of knowingly interfering with the exchange or use of electronic health information.

ASCO said that while some information-blocking results from efforts to protect privacy and security, other more troubling developments are occurring, including:

- per-transaction fees for each import or export of information to a different platform for electronic health information
- refusal to establish connections to permit information exchange with systems developed by competitors
- technological limits to the amount of historical information that can be exported to a recipient on a different company’s EHR platform
- contractual requirements that give an EHR company exclusive license to use a provider’s data.

In July, the House of Representatives passed the 21st Century Cures Act, which contains language addressing interoperability concerns, an action that Dr. Vose said was “significant.”

“We ask that the Senate adopt that language because further delay in this effort will be detrimental to patient care,” she said.
**Medscape**

**UTI agent appears efficacious in chronic prostatitis patients**

**For chronic prostatitis** patients who are resistant to first-line fluoroquinolones, high cure rates can be achieved with the urinary tract infection treatment fosfomycin (Monurol), according to research presented at the International Conference of Antimicrobial Agents and Chemotherapy in San Diego.

The authors evaluated outpatients with chronic prostatitis treated between November 2013 and March 2015. Of the 20 outpatients, 65% were infected with *Escherichia coli*, 15% with *Klebsiella oxytoca*, 10% with *Proteus mirabilis*, and 10% with *Enterococcus faecalis*.

Of these, 75% were resistant to fluoroquinolones, but all were susceptible to fosfomycin.

**Healthday News**

**Mushroom powder may reduce PSA in biochemically recurrent PCa patients**

**White button mushroom (WBM)** powder may reduce PSA levels in patients with biochemically recurrent prostate cancer, according to a study published in *Cancer* (2015; 121:2942-50).

Researchers from the City of Hope National Medical Center in Duarte, CA examined the effect of WBM powder on serum PSA in a study involving 36 prostate cancer patients with continuously rising PSA levels.

Overall response rate of PSA was 11%, and 36% of patients experienced some PSA decrease below baseline after 3 months of therapy.

“Therapy with WBM appears to both impact PSA levels and modulate the biology of biochemically recurrent prostate cancer by decreasing immunosuppressive factors,” the authors wrote.

**MedPage Today**

**Yohimbe supplement may contain pharmaceutical-grade ingredients**

**Yohimbe**, a botanical supplement, is being sold as pharmaceutical grade without patients’ knowledge, according to a recent study.

In an analysis of 49 brands of the supplement, about 40% didn’t contain other alkaloids that would be commonly found in yohimbe extract, which suggests a highly processed form of the active ingredient yohimbine.

“If you have yohimbine that’s highly refined to higher-than-prescription doses, you’re selling a drug,” said first author Pieter Cohen, MD, of Cambridge Health Alliance, Cambridge, MA.

The researchers’ findings were published online in *Drug Testing and Analysis* (Sept. 22, 2015).

**News Oddities**

**Finger length and prostate Ca risk: A valid link?**

**Finger length may affect lifetime risk of prostate cancer**, according to an article on Cleveland Clinic’s Health Essentials blog.

The idea that a longer ring finger than index finger increases risk started with basic observation and has picked up credibility in recent years, writes Charis Eng, MD, PhD, of Cleveland Clinic’s Genomic Medicine Institute.

In 2011, researchers analyzed more than 1,500 prostate cancer patients and 3,000 healthy control subjects over 15 years (*Br J Cancer* 2011; 104:175-7). Those whose index fingers were longer than their ring fingers had a 33% reduction in risk for prostate cancer.

In addition, further research has shown that the opposite—when ring fingers are longer than index fingers—is also associated with a higher detection rate of prostate cancer.

The reason for the link may come from *HOX* genes, as they play a role in the development of the prostate and kidneys, as well as fingers. *HOX* genes are out of proportion in prostate cancer tumors, researchers recently reported (*Oncol Rep* 2015; 34:1203-10).

“Studying *HOX* could lead to targeted therapies, in addition to ways to diagnose cases,” Dr. Eng wrote.
**WARNINGS AND PRECAUTIONS**

**Seizure**

In Study 1, which enrolled patients who previously received docetaxel, 7 of 809 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 251 days after initiation of XTANDI. In Study 2, 1 of 871 (0.1%) chemotherapynaive patients treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizure.

Limited safety data are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, and brain arteriovenous malformation. Study 1 excluded the use of concomitant medications that may lower the seizure threshold, whereas Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. (See Adverse Reactions (6.2)). PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

**ADVERSE REACTIONS**

**Clinical Trial Experience**

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

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

**Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy**

Study 1 enrolled 1,199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

**Table 1. Adverse Reactions in Study 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI N = 399</th>
<th>Placebo N = 399</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenic Disorders</td>
<td>14.0 11.0 1.0 5.1 1.0</td>
<td>22.0 15.0 2.5 2.5 0.5</td>
<td>7.9 0.5 0.0 0.0 0.0</td>
<td>3.0 2.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>General Disorders</td>
<td>11.0 9.0 0.5 0.0 0.0</td>
<td>16.0 12.0 0.5 0.0 0.0</td>
<td>6.0 1.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>7.0 5.0 0.0 0.0 0.0</td>
<td>11.0 8.0 0.0 0.0 0.0</td>
<td>4.0 0.0 0.0 0.0 0.0</td>
<td>1.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.0 7.0 1.0 0.0 0.0</td>
<td>13.0 10.0 0.0 0.0 0.0</td>
<td>3.0 2.0 0.0 0.0 0.0</td>
<td>1.0 1.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Metabolic Disorders</td>
<td>5.0 4.0 0.0 0.0 0.0</td>
<td>8.0 6.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>10.0 8.0 0.0 0.0 0.0</td>
<td>14.0 11.0 0.0 0.0 0.0</td>
<td>4.0 1.0 0.0 0.0 0.0</td>
<td>1.0 1.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>5.0 4.0 0.0 0.0 0.0</td>
<td>8.0 6.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>17.0 14.0 2.0 1.0 0.0</td>
<td>23.0 19.0 1.0 1.0 0.0</td>
<td>6.0 2.0 0.0 0.0 0.0</td>
<td>1.0 1.0 0.0 0.0 0.0</td>
</tr>
</tbody>
</table>

**Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer**

Study 2 enrolled 1,717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1,715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 31% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

**Table 2. Adverse Reactions in Study 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI N = 871</th>
<th>Placebo N = 844</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenic Disorders</td>
<td>15.0 12.0 1.0 0.0 0.0</td>
<td>17.0 15.0 1.0 1.0 0.0</td>
<td>7.0 1.0 0.0 0.0 0.0</td>
<td>2.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>General Disorders</td>
<td>20.0 17.0 1.0 1.0 0.0</td>
<td>25.0 22.0 1.0 1.0 0.0</td>
<td>6.0 1.0 0.0 0.0 0.0</td>
<td>1.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>6.0 5.0 0.0 0.0 0.0</td>
<td>9.0 7.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.0 8.0 1.0 0.0 0.0</td>
<td>14.0 11.0 1.0 1.0 0.0</td>
<td>3.0 1.0 0.0 0.0 0.0</td>
<td>1.0 1.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Metabolic Disorders</td>
<td>5.0 4.0 0.0 0.0 0.0</td>
<td>8.0 6.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>7.0 5.0 0.0 0.0 0.0</td>
<td>10.0 8.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>5.0 4.0 0.0 0.0 0.0</td>
<td>8.0 6.0 0.0 0.0 0.0</td>
<td>2.0 1.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>12.0 10.0 2.0 1.0 0.0</td>
<td>16.0 14.0 1.0 1.0 0.0</td>
<td>4.0 2.0 0.0 0.0 0.0</td>
<td>1.0 1.0 0.0 0.0 0.0</td>
</tr>
</tbody>
</table>

**Respiratory Disorders**

Epistaxis 10.0 8.0 1.0 0.0 0.0

**Other Disorders**

PTSD 11.0 9.0 1.0 0.0 0.0

**Contraindications**

XTANDI is contraindicated in pregnant women based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss.
If co-administration of XTANDI with a strong CYP2C8 inhibitor should be avoided if possible. Selection of a concomitant medication with no or minimal potential for serious adverse reactions in nursing infants or feed should be avoided if possible.

Laboratory Abnormalities

In the two randomized clinical trials, Grade 1–4 neutropenia occurred in 32% of patients treated with XTANDI (1% Grade 3–4) and in 6% of patients treated with placebo (0.5% Grade 3–4). The incidence of Grade 1–4 thrombocytopenia was 8% of patients treated with XTANDI (0.3% Grade 3–4) and 5% of patients treated with placebo (0.5% Grade 3–4). Grade 1–4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3–4) and 16% of patients treated with placebo (0.2% Grade 3–4). Grade 1–4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3–4) and 2% of patients treated with placebo (no Grade 3–4).

Falls

In the two randomized clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI and 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension

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

Post-Marketing Experience

The following additional adverse reactions have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

DISEASES

Diseases that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (e.g., carbamazepine, phenobarbital, phenytoin, or rifampin) may alter the plasma exposure of XTANDI and should be avoided if possible.

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

Risk Summary

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no human data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. XTANDI is contraindicated in women who are or may become pregnant while receiving XTANDI. If this drug is used during pregnancy, advise the patient to discontinue XTANDI, and apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6–15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10, and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6–19) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

To the extent that XTANDI can cause pregnancy loss, advise the patient to discontinue XTANDI and apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss.

Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use

Of 1671 patients who received XTANDI in the two randomized clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment

A dedicated renal impairment trial compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Baseline severe hepatic impairment (Child-Pugh Class C) has not been assessed.

OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported at ≥ 240 mg daily. Patients may be at increased risk of severe following:

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (Tk) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 28-week rat study, anaphylactic shock, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypoperfusion of the liver and atrophy of the liver and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062
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076-1119-PM
**Important Safety Information**

**Contraindications**  XTANDI is not indicated for women and is contraindicated in women who are or may become pregnant. XTANDI can cause fetal harm when administered to a pregnant woman.

**Warnings and Precautions**

**Seizure**  In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of XTANDI patients and 0% of placebo patients. In Study 2, conducted in patients with chemotherapy-naive metastatic CRPC, seizure occurred in 0.1% of XTANDI patients and 0.1% of placebo patients. There is no clinical trial experience readministering XTANDI to patients who experienced a seizure, and limited safety data are available in patients with predisposing factors for seizure. Study 1 excluded the use of concomitant medications that may lower threshold; Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity during which sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

**Adverse Reactions**

The most common adverse reactions (≥ 10%) reported from two combined clinical studies that occurred more commonly (≥ 2% over placebo) in XTANDI patients were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In Study 1, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In Study 2, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups.

- **Lab Abnormalities**: Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

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

- **Falls (including fall-related injuries)**, occurred in 9% of XTANDI patients and 4% of placebo patients. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

- **Hypertension** occurred in 11% of XTANDI patients and 4% of placebo patients. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of all patients.

**Drug Interactions**

**Effect of Other Drugs on XTANDI**  Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration cannot be avoided, reduce the dose of XTANDI.

Avoid strong or moderate CYP3A4 or CYP2C8 inducers as they can alter the plasma exposure to XTANDI.

**Effect of XTANDI on Other Drugs**  Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

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

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94% of insured patient lives are covered for XTANDI*2

*As of February 2015. A product’s placement on a plan formulary involves a variety of factors known only to the plan and is subject to eligibility.

To learn more, please visit XtandiHCP.com
XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Select Safety Information

XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Seizure occurred in 0.9% of patients receiving XTANDI who previously received docetaxel and in 0.1% of patients who were chemotherapy-naive. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

There have been post approval reports of posterior reversible encephalopathy syndrome (PRES), a neurological disorder which can present with rapidly evolving symptoms and requires confirmation by brain imaging. Discontinue XTANDI in patients who develop PRES.


Please see inside page for additional Important Safety Information.
Please see adjacent pages for Brief Summary of Full Prescribing Information.