Who is XTANDI for? XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. (This is a type of advanced prostate cancer.)

Select Safety Information
Who should not take XTANDI? XTANDI is not for use in women. Women should not take XTANDI if they are pregnant or may become pregnant. XTANDI can harm an unborn baby. It is not known if XTANDI is safe and effective in children.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
YOUR GUIDE TO STARTING XTANDI

Inside you’ll find information about starting XTANDI (ex-TAN-dee) and how it may be able to help fight advanced prostate cancer.

About XTANDI 3
How XTANDI May Help 7
Side Effects 9
Taking XTANDI 11
How to Get XTANDI 16
XTANDI Support Solutions™ 19
Help With Managing Weakness or Feeling Tired 21
Important Safety Information 24
Questions to Ask Your Healthcare Team 29

XTANDI Support Solutions is dedicated to helping you get the support you need to get started on XTANDI. Get the details on page 19.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
ABOUT XTANDI

- XTANDI is FDA-approved to treat men with a type of advanced prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

- XTANDI was researched in one study to find out if it may help men live longer and/or slow cancer progression. Learn about these results on page 7.

- XTANDI was researched in an additional study against another common treatment for advanced prostate cancer. Learn about these results on page 8.

- XTANDI may cause side effects—learn more on page 9. Talk with your healthcare team about any side effect that bothers you, or you may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- Steroids, for example oral prednisone, can be taken but are not required with XTANDI. Talk with your urologist or oncologist if you have questions about steroids.

Answers to your XTANDI questions are just a phone call away.
Call 1-855-8XTANDI (1-855-898-2634) anytime.
Understanding advanced prostate cancer and XTANDI

When prostate cancer first develops, it is only found in the prostate. But sometimes even with treatment to control the cancer, it can get worse or advance.

XTANDI is FDA-approved to treat a type of advanced prostate cancer that:

- No longer responds to a medical or surgical treatment that lowers testosterone, and
- Has spread, or metastasized, beyond the prostate to other areas of the body

Important safety information to tell your doctor before starting XTANDI

Before you take XTANDI, tell your doctor if you have a history of seizures, brain injury, stroke, or brain tumors; have any other medical conditions; or have a pregnant partner or a partner who may become pregnant. Tell your doctor if you take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. You should not start or stop any medicine before you talk with your doctor.
David, treated with XTANDI
Go to XTANDI.com/videos to watch David’s XTANDI story.
**How XTANDI is thought to work within prostate cancer cells**

XTANDI is what is called an androgen receptor inhibitor. Androgens are a group of hormones that includes testosterone. Androgen receptor inhibitors interfere with the connection between androgens and androgen receptors. This can help slow cancer cell growth.

*Imagine the inside of a prostate cancer cell as a puzzle:*

**Prostate cancer cell**

When the androgen connects with the androgen receptor, it may cause the tumor cells to grow.

**XTANDI in a prostate cancer cell**

Decreasing how often the androgen can connect with the androgen receptor may reduce tumor growth.

This is how XTANDI was shown to work in laboratory studies.

**As a result, the cancer cells may die and the prostate tumor may stop growing.**

**Select Safety Information**

If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
HOW XTANDI MAY HELP

XTANDI fights advanced prostate cancer
A study of 1,717 men with advanced prostate cancer compared men taking XTANDI with men not taking XTANDI. These men had not received treatment with chemotherapy and had prostate cancer that had spread to other parts of the body. Men also received hormone therapy injections during the course of this study.

During this study, XTANDI:

- **Slowed the progression of advanced prostate cancer**
  Men taking XTANDI had an 83% lower chance of their cancer progressing compared with men not taking XTANDI.*

- **Helped men live longer**
  Men taking XTANDI lived longer than men not taking XTANDI. The median overall survival was 35 months for men taking XTANDI vs 31 months for men not taking XTANDI.

During the study, XTANDI also delayed the time to start chemotherapy
XTANDI delayed the time before patients began chemotherapy by a median of 28 months vs 11 months for men not taking XTANDI. The median is the middle number of a group of numbers.

*In this study, 86% of patients taking XTANDI did not see their cancer get worse vs 60% of patients not taking XTANDI. In the study, progression was defined as the cancer getting worse, as measured by scans, or if the patient died for any reason.

Select Safety Information
If you take XTANDI you may be at risk of developing a condition involving the brain called Posterior Reversible Encephalopathy Syndrome (PRES). Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.
XTANDI was also studied to understand how well it slows progression when compared against bicalutamide

A study of 375 men with advanced prostate cancer compared 184 men who were taking XTANDI with 191 men who were taking bicalutamide. These men had not received treatment with chemotherapy and had prostate cancer that had spread to other parts of the body. Men also received hormone therapy injections during the course of this study.

**During this study, XTANDI slowed the progression of advanced prostate cancer compared with bicalutamide**

Men taking XTANDI had a 40% lower chance of their cancer progressing than men taking bicalutamide.*

**Select Safety Information**

In this study, the most common side effects patients taking XTANDI experienced more than patients taking bicalutamide were fatigue, hot flashes, high blood pressure, diarrhea, weight loss, and pain in the extremities.

*In the study, progression was defined as the cancer getting worse, as measured by scans, or if the patient died for any reason.

Talk with your doctor or call XTANDI Support Solutions at 1-855-8XTANDI (1-855-898-2634) to learn more.
SIDE EFFECTS

**XTANDI may cause serious side effects**

If you take XTANDI, you may be at risk of having a seizure.

- In studies comparing XTANDI with placebo, 8 out of 1,671 patients taking XTANDI had a seizure and 1 out of 1,243 patients taking placebo had a seizure

- In a separate study comparing XTANDI with bicalutamide, 3 out of 380 patients taking XTANDI had a seizure and 1 out of 387 patients taking bicalutamide had a seizure

Avoid activities where losing consciousness could seriously harm you or someone else. Tell your doctor right away if you lose consciousness or have a seizure. Your doctor will stop XTANDI if you have a seizure during treatment.

**Since XTANDI was FDA-approved in 2012, there have been reports of XTANDI patients developing a condition involving the brain called Posterior Reversible Encephalopathy Syndrome (PRES).**

Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

Looking for help? Tips for managing weakness or feeling tired are on page 21.
The most common side effects of XTANDI

- Weakness or feeling more tired than usual
- Back pain
- Decreased appetite
- Constipation
- Joint pain
- Diarrhea
- Hot flashes
- Upper respiratory tract infection
- Swelling in your hands, arms, legs, or feet
- Shortness of breath
- Muscle and bone pain
- Weight loss
- Headache
- High blood pressure
- Dizziness
- A feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls, and injuries from falls. Tell your doctor if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
TAKING XTANDI

What to tell your doctor before starting XTANDI

Tell your doctor if you:

Have a history of seizures, brain injury, stroke, or brain tumors

Have any other medical conditions

Have a partner who is pregnant or may become pregnant

- If you are sexually active with a pregnant woman, you must use a condom during treatment with XTANDI and for 3 months after treatment
- If you have a partner who may become pregnant, use a condom and another form of birth control during treatment with XTANDI and for 3 months after treatment

Take other medicines

XTANDI may affect the way other medicines work, and other medicines may affect the way XTANDI works. That’s why it’s important to tell your doctor about all the medicines you take. This includes prescription and over-the-counter medicines, including vitamins and herbal supplements. Keep a list of all your medications, and inform your doctor before making any changes to your treatment routine.
How to take XTANDI

XTANDI is taken once a day, at the same time each day. It’s important to take XTANDI exactly as prescribed by your doctor.

- The recommended dose of XTANDI is four 40-mg capsules, for a total dose of 160 mg. Your doctor will change your dose if needed. Do not change or stop taking your prescribed dose of XTANDI without talking with your doctor first.

- XTANDI must be swallowed whole with fluids, like water or juice. Do not chew, dissolve, or open the capsules.

- XTANDI can be taken with or without food. This gives you the flexibility to plan your daily dose around your own schedule. Just remember to take XTANDI at the same time each day.

Try the tips below to help you take your medicine as directed by your doctor:

- Take XTANDI when you do another daily activity, such as after brushing your teeth.
- Download the XTANDI treatment tracking calendar on XTANDI.com/calendar.
- Set an alarm to help you remember to take XTANDI at the same time each day.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
## TAKING XTANDI

### What to do if you miss a dose

<table>
<thead>
<tr>
<th>Missed your regular treatment time</th>
<th>Take XTANDI as soon as you remember that same day.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed by 1 day</td>
<td>Take your normal dose of XTANDI at your regular time the next day.</td>
</tr>
</tbody>
</table>

Remember, you should only take your prescribed dose of XTANDI once per day. **If you take too much XTANDI in 1 day, contact a member of your healthcare team or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.**

---

“**My doctor told me that as long I take XTANDI daily, I can take it before a meal or after a meal.**”

—David, treated with XTANDI

Go to XTANDI.com/videos to watch David’s XTANDI story.
Assessing your prostate cancer while taking XTANDI

A PSA (prostate-specific antigen) test is often used to help diagnose prostate cancer, and it can also be used after diagnosis to help monitor your cancer response or progression. Although a PSA test can be helpful, it will not provide you and your doctor with a complete picture of your cancer. Aside from a PSA test, other tests—such as a computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, or a bone scan—and physical exams can help your doctor assess your cancer.

Did you know?

Because a single PSA test will not give you a complete picture of your cancer, it’s important to talk with your doctor about other tests that can be used to monitor your prostate cancer.

How to store XTANDI

Store XTANDI in a dry place that stays between 68°F and 77°F (20°C and 25°C). Always keep XTANDI dry and in a tightly closed container, and out of the reach of children.
Dennis, treated with XTANDI
Go to XTANDI.com/videos to watch Dennis's XTANDI story.

Please see Important Safety Information for XTANDI (enzalutamide) capsules on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
HOW TO GET XTANDI

There are 2 ways to get XTANDI:

It’s important to know that XTANDI is not available at your local drugstore.

1 **Specialty pharmacy**
   In most cases, your doctor will send your XTANDI prescription to a specialty pharmacy. A specialty pharmacy fills prescriptions for certain medicines that are not available at regular drugstores. One benefit of getting XTANDI from a specialty pharmacy is that your medicine will be mailed right to your home. The specialty pharmacy will call you to arrange the delivery of your medicine.

   Specialty pharmacies may also offer other services to assist you. These include helping you understand your insurance coverage and finding programs that may offer financial assistance if you can’t afford your co-pay or medicine.* They can also provide you with helpful information about XTANDI.

2 **Pharmacy in your doctor’s office**
   In some cases, your doctor’s office may have its own pharmacy that can fill your XTANDI prescription.

*Subject to eligibility. Restrictions may apply.

---

Our dedicated access specialists at XTANDI Support Solutions can help you get XTANDI.

Go to page 19 or call 1-855-8XTANDI (1-855-898-2634) to learn more.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
HOW TO GET XTANDI

Getting XTANDI from a specialty pharmacy

Here’s how the process typically works, and a few tips to help ensure it goes as smoothly as possible.

At your doctor’s office: A member of your healthcare team will fill out the required insurance paperwork with you and then send your prescription for XTANDI to a specialty pharmacy or XTANDI Support Solutions to help with the process.

Tip At your appointment, confirm that your insurance paperwork is complete.

A few days after your appointment: The specialty pharmacy will call you about your out-of-pocket costs and arrange the delivery of your medicine. You may also receive a call from XTANDI Support Solutions if there are any questions with the insurance paperwork.

Tip Reach out to your doctor if you haven’t heard from your specialty pharmacy within a few days.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
HOW TO GET XTANDI

Getting XTANDI from a specialty pharmacy (continued)

Here’s how the process typically works, and a few tips to help ensure it goes as smoothly as possible.

When it’s time for delivery: XTANDI may be delivered right to your home or office.

When it’s time for a refill: Your specialty pharmacy will call you to arrange a refill.

Tip If you haven’t received your medicine, call your healthcare provider or specialty pharmacy.

Tip Contact your specialty pharmacy 2 weeks before your medicine is going to run out if you have not heard from them.

XTANDI Support Solutions can help you get XTANDI.

All you have to do is call 1-855-8XTANDI (1-855-898-2634). Our dedicated access specialists are here to help.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
XTANDI SUPPORT SOLUTIONS

One phone number, lots of answers—call 1-855-8XTANDI (1-855-898-2634)

XTANDI Support Solutions is dedicated to helping you get the support you need. With us, you’ll have 24/7 access to resources to help you get started on XTANDI and stay on track. Whether you need help finding financial assistance or have questions about XTANDI, call 1-855-8XTANDI (1-855-898-2634) to get in touch with a dedicated access specialist or nurse.

Help getting and paying for XTANDI

Our dedicated access specialists can help you navigate the process of getting started on XTANDI, from arranging the delivery of your medicine to helping you find ways to pay for it.* They are available Monday through Friday from 8 AM to 8 PM ET.

Our dedicated access specialists also can assist in finding you financial support based on your unique situation:
• If you are a new patient or your insurance changes
• If you have insurance from your employer or you are self-insured
• If you don’t have insurance or XTANDI is not covered
• If you have Medicare, Medicaid, or TriCare®

Pay no more than $20 per month for your XTANDI prescription.* Call XTANDI Support Solutions at 1-855-8XTANDI (1-855-898-2634) to find out if you qualify.

*Subject to eligibility. Restrictions may apply.

Please see Important Safety Information for XTANDI on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
24/7 phone support from our team of nurses

Call anytime to speak with a nurse who is working on behalf of Astellas and Medivation. **Talking to our nurses should not replace the advice of your healthcare team.** Our nurses are available day and night to help answer your questions about:

- How XTANDI works
- Taking XTANDI
- Adding XTANDI to your daily routine
- How XTANDI may help
- Possible side effects of XTANDI*

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

—Theresa, caring for her husband Dennis

Go to XTANDI.com/videos to watch Theresa’s story.

It’s great to know someone is there who can help answer your questions about XTANDI 24/7. “
HELP WITH MANAGING WEAKNESS OR FEELING TIRED

**Tips to discuss with your doctor**
These tips come from organizations that focus on supporting people with cancer. These tips have not been studied with XTANDI (enzalutamide) capsules, but they may be able to help you manage weakness or feeling tired. You should always talk with your healthcare team before deciding if any of these tips are right for you.

**Weakness**

- **Drink plenty of fluids, especially water.**
  Your body needs water to do its work. Talk to your healthcare team about how much water to drink each day.

- **Stay active.**
  Try going for short walks or doing light stretching exercises. Talk with your healthcare team about other types of exercise that may help you feel better.

- **Get a good night’s sleep.**
  If you feel tired during the day, it’s okay to rest and take a nap. Try to keep your naps short and early in the day so they don’t interfere with nighttime sleep.
HELP WITH MANAGING WEAKNESS OR FEELING TIRED

**Feeling tired**

- **Try to exercise.**
  Exercise can help you feel better both physically and mentally. If you decide to exercise, make sure to check with your doctor about healthy ways to add it to your routine.

- **Focus on relaxing.**
  If you’re feeling stressed, it might help if you talk to other men living with advanced prostate cancer. Support groups can be a great place to start. You can also try doing things that can help you relax but that require little energy, like reading, listening to music, or meditating.

- **Stick with a consistent sleep schedule.**
  Try to sleep 7 to 8 hours each night. Also, try to limit your naps to under 30 minutes. If you can, avoid foods and drinks that are high in caffeine at night.

- **Talk with your healthcare team or dietician about managing your diet.**
  Work with them to create an eating plan that includes the right amount of nutrients and fluids your body needs.
Theresa, caring for her husband Dennis
Go to XTANDI.com/videos to watch Theresa’s XTANDI story.

Please see Important Safety Information for XTANDI (enzalutamide) capsules on pages 24-28 and accompanying Full Prescribing Information on pages 32-54.
WHAT IS XTANDI?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

WHO SHOULD NOT TAKE XTANDI?

XTANDI is not for use in women. Women should not take XTANDI if they are pregnant or may become pregnant. XTANDI can harm an unborn baby. It is not known if XTANDI is safe and effective in children.
WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING XTANDI?

Tell your doctor if you:

- Have a history of seizures, brain injury, stroke, or brain tumors
- Have any other medical conditions
- Have a partner who is pregnant or may become pregnant
  
  **If you have a pregnant partner,** it’s important to know that XTANDI can harm a baby in the womb. If you are sexually active with a pregnant woman, you must use a condom during treatment. Also use a condom for 3 months after treatment with XTANDI.
  
  **If you have a partner who may become pregnant,** use a condom and another form of birth control while taking XTANDI. If you stop taking XTANDI, you should keep using 2 forms of birth control for at least 3 months before planning a pregnancy. Talk with your doctor if you have questions about birth control.

- Take other medicines
  
  XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. These include prescription and over-the-counter medicines, vitamins, and herbal supplements. Do not start or stop any medicine without talking to your doctor.
HOW SHOULD I TAKE XTANDI?

Take XTANDI every day exactly as your doctor tells you
Take all your prescribed dose once a day, at the same time each day. Swallow XTANDI capsules whole. Do not chew, dissolve, or open the XTANDI capsules. XTANDI can be taken with or without food. Your doctor may change your dose if needed.

If you miss a dose of XTANDI:
Take your prescribed dose as soon as you remember that day. If you miss a daily dose, just take XTANDI at your regular time the next day. Do not take more than your prescribed dose in one day. If you take too much XTANDI, call your doctor or go to the nearest emergency room right away. Taking too much XTANDI may increase your risk of having a seizure.

Do not change or stop taking your prescribed dose of XTANDI without talking with your doctor first
WHAT ARE THE POSSIBLE SIDE EFFECTS OF XTANDI?

XTANDI may cause serious side effects including:

Seizure
If you take XTANDI you may be at risk of having a seizure. Avoid activities where losing consciousness could seriously harm you or someone else. Tell your doctor right away if you lose consciousness or have a seizure. Your doctor will stop XTANDI if you have a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)
If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.
The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- vertigo (a feeling that you or things around you are moving or spinning)

XTANDI may cause infections, falls and injuries from falls. Tell your doctor if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
QUESTIONS TO ASK YOUR HEALTHCARE TEAM

As you get started on XTANDI, it may be helpful to keep a list of questions to discuss with your healthcare team. Below are some questions to help you get started.

How do I take XTANDI?

How will I know if XTANDI is working for me?

Learn more For helpful resources, including organizations that offer support for men living with prostate cancer, visit XTANDI.com/resources
**QUESTIONS TO ASK YOUR HEALTHCARE TEAM**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the possible side effects of XTANDI?</td>
<td></td>
</tr>
<tr>
<td>What should I do if I experience a side effect of XTANDI?</td>
<td></td>
</tr>
<tr>
<td>How will I get XTANDI? Where can I find help paying for my medicine if I can’t afford it?</td>
<td></td>
</tr>
</tbody>
</table>
For more information about XTANDI, call 1-855-8XTANDI (1-855-898-2634) or visit XTANDI.com
XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

---------------------------RECENT MAJOR CHANGES---------------------------
Contraindications (4) 10/2016
Warnings and Precautions (5.1) 10/2016

---------------------------INDICATIONS AND USAGE--------------------------
XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

-----------------------DOSAGE AND ADMINISTRATION----------------------
XTANDI 160 mg (four 40 mg capsules) administered orally once daily. Swallow capsules whole. XTANDI can be taken with or without food. (2.1)

---------------------DOSAGE FORMS AND STRENGTHS---------------------
Capsule 40 mg (3)

----------------------------CONTRAINDICATIONS-------------------------------
Pregnancy (4, 8.1)

-------------------------WARNINGS AND PRECAUTIONS---------------------
• Seizure occurred in 0.5% of patients receiving XTANDI. There is no clinical trial experience with XTANDI in patients who have had a seizure. Permanently discontinue XTANDI in patients who develop a seizure during treatment. (5.1)
• Posterior reversible encephalopathy syndrome (PRES): Discontinue XTANDI. (5.2)

------------------------------ADVERSE REACTIONS------------------------------
The most common adverse reactions (≥10%) are 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----------------------------DRUG INTERACTIONS-------------------------------
• Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. (2.2, 7.1)
• Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI. (2.2, 7.2)
• 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. (7.3)

----------------------USE IN SPECIFIC POPULATIONS---------------------
• Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Dosing Information
  2.2 Dose Modifications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Seizure
  5.2 Posterior Reversible Encephalopathy Syndrome (PRES)
6 ADVERSE REACTIONS
  6.1 Clinical Trial Experience
  6.2 Post-Marketing Experience
7 DRUG INTERACTIONS
  7.1 Drugs that Inhibit CYP2C8
  7.2 Drugs that Induce CYP3A4
  7.3 Effect of XTANDI on Drug Metabolizing Enzymes
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal Impairment
8.7 Patients with Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
XTANDI® is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information
The recommended dose of XTANDI is 160 mg (four 40 mg capsules) administered orally once daily. XTANDI can be taken with or without food [see Clinical Pharmacology (12.3)]. Swallow capsules whole. Do not chew, dissolve, or open the capsules.

2.2 Dose Modifications
If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Concomitant Strong CYP2C8 Inhibitors
The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the XTANDI dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

Concomitant Strong CYP3A4 Inducers
The concomitant use of strong CYP3A4 inducers should be avoided if possible. If patients must be co-administered a strong CYP3A4 inducer, increase the XTANDI dose from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS
XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ.

4 CONTRAINDICATIONS

Pregnancy
XTANDI can cause fetal harm and potential loss of pregnancy [see Use in Specific Populations (8.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Seizure
Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In placebo-controlled studies, 8 of 1671 (0.5%) patients treated with XTANDI and 1 of 1243 (0.1%) patients treated with placebo experienced a seizure. In patients who previously received docetaxel, 7 of 800 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In a placebo-controlled study in chemotherapy-naive patients, 1 of 871 (0.1%) treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. In bicalutamide-controlled studies conducted in chemotherapy-naive patients, 3 of 380 (0.8%) patients treated with XTANDI and 1 of 387 (0.3%) patients treated with bicalutamide 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.

Reference ID: 4001743
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.

5.2 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.

6 ADVERSE REACTIONS
The following is discussed in more detail in other sections of the labeling:
- Seizure [see Warnings and Precautions (5.1)]
- Posterior Reversible Encephalopathy Syndrome (PRES) [see Warnings and Precautions (5.2)]

6.1 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.

Three randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchiectomy), a disease setting that is also defined as metastatic CRPC. Two trials were placebo-controlled (Studies 1 and 2), and one trial was bicalutamide-controlled (Study 3). In Studies 1 and 2, patients received XTANDI 160 mg or placebo orally once daily. In Study 3, patients received XTANDI 160 mg or bicalutamide 50 mg orally once daily. 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 placebo-controlled 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: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy
Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

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

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 800</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>50.6</td>
<td>9.0</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>15.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculoskeletal And Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>26.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>15.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>9.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Musculoskeletal Stiffness</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>20.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Spinal Cord Compression and Cauda Equina Syndrome</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>4.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Infections And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>10.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection</td>
<td>8.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Renal And Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>6.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>4.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Injury, Poisoning And Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>4.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Non-pathologic Fractures</td>
<td>4.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>3.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Study 2: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

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

Table 2. Adverse Reactions in Study 2

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 871</th>
<th>Placebo N = 844</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3.3</td>
<td>0.1</td>
</tr>
<tr>
<td>a CTCAE v4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Includes asthenia and fatigue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c Includes dizziness and vertigo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>46.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>11.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Musculoskeletal And Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>28.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>18.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Headache</td>
<td>11.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Mental Impairment</td>
<td>5.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Infections And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract</td>
<td>16.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>XTANDI N = 871</td>
<td>Placebo N = 844</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Infection&lt;sup&gt;f&lt;/sup&gt;</td>
<td>7.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Renal And Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>8.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Injury, Poisoning And Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>12.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Non-Pathological Fracture</td>
<td>8.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>18.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Reproductive System and Breast disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>3.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

**Study 3: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC**

Study 3 enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.
<table>
<thead>
<tr>
<th>Table 3. Adverse Reactions in Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>XTANDI (N=183)</td>
</tr>
<tr>
<td>Grade 1-4&lt;sup&gt;a&lt;/sup&gt; (%)</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
</tr>
<tr>
<td>Asthenic Conditions&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Musculoskeletal And Connective Tissue Disorders</strong></td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Musculoskeletal Pain&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
</tr>
<tr>
<td>Hot Flush</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td><strong>Infections And Infestations</strong></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Investigational</strong></td>
</tr>
<tr>
<td>Weight Loss</td>
</tr>
</tbody>
</table>

<sup>a</sup> CTCAE v 4
<sup>b</sup> Including asthenia and fatigue.
<sup>c</sup> Including musculoskeletal pain and pain in extremity
<sup>d</sup> Including nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis

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

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

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

Reference ID: 4001743
**Hypertension**
In the two randomized placebo-controlled 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.

**6.2 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)*

**7 DRUG INTERACTIONS**

7.1 **Drugs that Inhibit CYP2C8**
Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

7.2 **Drugs that Induce CYP3A4**
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

7.3 **Effect of XTANDI on Drug Metabolizing Enzymes**
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring [see Clinical Pharmacology (12.3)].

**8 USE IN SPECIFIC POPULATIONS**

8.1 **Pregnancy**

**Risk Summary**
XTANDI is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. XTANDI is not indicated for use in females. There are no human data on the use of XTANDI in pregnant women. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose [see Data].
Data

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

8.2 Lactation

Risk Summary
XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.

8.3 Females and Males of Reproductive Potential

Contraception
Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of XTANDI [see Use in Specific Populations (8.1)].

Infertility
Based on animal studies, XTANDI may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

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

8.5 Geriatric Use
Of 1671 patients who received XTANDI in the two randomized placebo-controlled 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.

8.6 Patients with Renal Impairment
A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed [see Clinical Pharmacology (12.3)].
8.7 Patients with Hepatic Impairment
Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE
In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

11 DESCRIPTION
Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluoro-N-methylbenzamide.

The molecular weight is 464.44 and molecular formula is C_{21}H_{16}F_{4}N_{4}O_{2}S. The structural formula is:

![Structural formula of enzalutamide]

Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocapryl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro, and decreased tumor volume in a mouse prostate cancer xenograft model.

12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with metastatic CRPC. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia
correction method. However, small increases in the mean QTc interval (i.e., less than 10 ms) due to enzalutamide cannot be excluded due to limitations of the study design.

12.3 Pharmacokinetics
The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic CRPC and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption
Following oral administration (XTANDI 160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations (C_max) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_max values for enzalutamide and N-desmethyl enzalutamide are 16.6 μg/mL (23% CV) and 12.7 μg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 μg/mL (26% CV) and 13.0 μg/mL (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide. The results are summarized in Figure 1.

Distribution and Protein Binding
The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins. In vitro, there was no protein binding displacement between enzalutamide and other highly protein bound drugs (warfarin, ibuprofen, and salicylic acid) at clinically relevant concentrations.

Metabolism
Following single oral administration of 14C-enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the 14C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total 14C-AUC_0-inf.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on in vivo and in vitro data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

In vitro, N-desmethyl enzalutamide is not a substrate of human CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5.

Elimination
Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of 14C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).
The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life (t\textsubscript{1/2}) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal t\textsubscript{1/2} for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

**Pharmacokinetics in Special Populations**

**Renal Impairment:**
A population pharmacokinetic analysis (based on pre-existing renal function) was carried out with data from 59 healthy male volunteers and 926 patients with metastatic CRPC enrolled in clinical trials, including 512 with normal renal function (CrCL \geq 90 mL/min), 332 with mild renal impairment (CrCL 60 to < 90 mL/min), 88 with moderate renal impairment (CrCL 30 to < 60 mL/min), and 1 with severe renal impairment (CrCL < 30 mL/min). The apparent clearance of enzalutamide was similar in patients with pre-existing mild and moderate renal impairment (CrCL 30 to < 90 mL/min) compared to patients and volunteers with normal renal function. The potential effect of severe renal impairment or end stage renal disease on enzalutamide pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient [see Use in Specific Populations (8.6)].

**Hepatic Impairment:**
The plasma pharmacokinetics of enzalutamide and N-desmethyl enzalutamide were examined in volunteers with normal hepatic function (N = 22) and with pre-existing mild (N = 8, Child-Pugh Class A) moderate (N = 8, Child-Pugh B), or severe (N = 8, Child-Pugh C) hepatic impairment. XTANDI was administered as a single 160 mg dose. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. The results are summarized in Figure 1 [see Use in Specific Populations (8.7)].

**Body Weight and Age:**
Population pharmacokinetic analyses showed that weight (range: 46 to 163 kg) and age (range: 41 to 92 yr) do not have a clinically meaningful influence on the exposure to enzalutamide.

**Gender:**
The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated.

**Race:**
The majority of XTANDI-treated patients in the randomized clinical trials were Caucasian (85%). Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

**Drug Interactions**

**Effect of Other Drugs on XTANDI:**
In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the AUC\textsubscript{0-inf} of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C\textsubscript{max}. The results are summarized in Figure 1 [see Dosage and Administration (2.2) and Drug Interactions (7.1)].
In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer). Rifampin decreased the AUC0-inf of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on Cmax. The results are summarized in Figure 1 [see Dosage and Administration (2.2) and Drug Interactions (7.2)].

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the AUC0-inf of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on Cmax. The results are summarized in Figure 1.

**Figure 1. Effects of Other Drugs and Intrinsic/Extrinsic Factors on XTANDI**

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK**</th>
<th>Fold Change and 90% Confidence Interval</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2C8 Inhibitor,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID</td>
<td>Cmax</td>
<td></td>
<td>Reduce XTANDI dose*</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitor,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg QD</td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 Inducer,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg QD</td>
<td>Cmax</td>
<td></td>
<td>Increase XTANDI dose*</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment, Mild (Child-Pugh A)</td>
<td>Cmax</td>
<td></td>
<td>No initial dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment, Moderate (Child-Pugh B)</td>
<td>Cmax</td>
<td></td>
<td>No initial dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment, Severe (Child-Pugh C)</td>
<td>Cmax</td>
<td></td>
<td>No initial dose adjustment</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
<td>Take with or without food</td>
</tr>
<tr>
<td>High-fat Meal</td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PK parameters (Cmax and AUC0-inf) are for enzalutamide plus N-desmethyl enzalutamide, except in the food-effect trial, where they are for enzalutamide alone.

* See Dosage and Administration (2.2).
Effect of XTANDI on Other Drugs:
In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with metastatic CRPC, a single oral dose of the CYP probe substrate cocktail (for CYP2C8, CYP2C9, CYP2C19, and CYP3A4) was administered before and concomitantly with XTANDI (following at least 55 days of dosing at 160 mg daily). The results are summarized in Figure 2. Results showed that *in vivo*, at steady state, XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer [see Drug Interactions (7.3)]. XTANDI did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with CRPC, a single oral dose of the CYP probe substrate cocktail for CYP1A2 and CYP2D6 was administered before and concomitantly with XTANDI (following at least 49 days of dosing at 160 mg daily). The results are summarized in Figure 2. Results showed that *in vivo*, at steady state, XTANDI did not cause clinically meaningful changes in exposure to the CYP1A2 or CYP2D6 substrates.

Figure 2. Effect of XTANDI on Other Drugs

![Figure 2](image)

*See Drug Interactions (7.3).

*In vitro*, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; however, subsequent clinical data showed that XTANDI is an inducer of CYP2C9, CYP2C19, and CYP3A4 and had no clinically meaningful effect on CYP2C8 (see Figure 2). *In vitro*, enzalutamide caused time-dependent inhibition of CYP1A2.

*In vitro* studies showed that enzalutamide induces CYP2B6 and CYP3A4 and does not induce CYP1A2 at therapeutically relevant concentrations.
In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for human P-glycoprotein. In vitro, enzalutamide and N-desmethyl enzalutamide are inhibitors of human P-glycoprotein, while the major inactive carboxylic acid metabolite is not.

In vitro, enzalutamide and N-desmethyl enzalutamide do not appear to be substrates of human breast cancer resistance protein (BCRP); however, enzalutamide and N-desmethyl enzalutamide are inhibitors of human BCRP at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

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

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES
The efficacy and safety of XTANDI in 3291 patients with metastatic CRPC were demonstrated in three randomized, multicenter clinical trials. All patients continued on GnRH therapy or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate glucocorticoids.

Study 1: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy
A total of 1199 patients who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a previous history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible [see Warnings and Precautions (5.1)].

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score of ≥ 4. Ninety-one percent of patients had metastases in bone and 23% had visceral involvement in the lung and/or liver. Fifty-nine percent of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis at the time of 520 deaths in patients on the XTANDI arm compared to patients on the placebo arm (Table 4 and Figure 3).

Reference ID: 4001743
Table 4. Overall Survival of Patients Treated with Either XTANDI or Placebo in Study 1

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 800</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Deaths (%)</td>
<td>308 (38.5%)</td>
<td>212 (53.1%)</td>
</tr>
<tr>
<td>Median Survival, months (95% CI)</td>
<td>18.4 (17.3, NR)</td>
<td>13.6 (11.3, 15.8)</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.63 (0.53, 0.75)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value is derived from a log-rank test stratified by baseline ECOG performance status score (0-1 vs. 2) and mean baseline pain score (BPI-SF score < 4 vs. ≥ 4)

<sup>b</sup> Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors XTANDI

NR denotes “not reached”.

Figure 3. Kaplan-Meier Overall Survival Curves in Study 1

Study 2: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

In Study 2, 1717 chemotherapy-naïve patients were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment
continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression) and the initiation of a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 42-93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% Other. The ECOG performance status score was 0 for 68% of patients, and 1 for 32% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 67% of patients, and 2-3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours at study entry). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Twelve percent of patients had visceral (lung and/or liver) disease involvement. During the study, 27% of patients on the XTANDI arm and 30% of patients on the placebo arm received glucocorticoids for varying reasons.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis, conducted after 540 deaths in patients treated with XTANDI compared to those treated with placebo (Table 5). Forty percent of XTANDI-treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 6, Figure 4). At the updated analysis, 52% of XTANDI-treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. XTANDI was used as a subsequent therapy in 2% of XTANDI-treated patients and 29% of placebo-treated patients.

### Table 5. Overall Survival of Patients Treated with Either XTANDI or Placebo in Study 2

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 872</th>
<th>Placebo N = 845</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-specified Interim Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Deaths (%)</td>
<td>241 (28%)</td>
<td>299 (35%)</td>
</tr>
<tr>
<td>Median Survival, months (95% CI)</td>
<td>32.4 (30.1, NR)</td>
<td>30.2 (28.0, NR)</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.71 (0.60, 0.84)</td>
<td></td>
</tr>
<tr>
<td><strong>Updated Survival Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Deaths (%)</td>
<td>368 (42%)</td>
<td>416 (49%)</td>
</tr>
<tr>
<td>Median Survival, months (95% CI)</td>
<td>35.3 (32.2, NR)</td>
<td>31.3 (28.8, 34.2)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.77 (0.67, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The data cutoff date is 16 Sep 2013
<sup>b</sup> P-value is derived from an unstratified log-rank test.
<sup>c</sup> Hazard ratio is derived from an unstratified proportional hazards model. Hazard ratio < 1 favors XTANDI.
<sup>d</sup> The data cutoff date is 1 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥765. NR denotes “not reached”.

Reference ID: 4001743
A statistically significant improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with placebo (Table 6, Figure 5).

Table 6. Radiographic Progression-free Survival of Patients Treated with Either XTANDI or Placebo in Study 2

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 832</th>
<th>Placebo N = 801</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Progression or Deaths (%)</td>
<td>118 (14%)</td>
<td>320 (40%)</td>
</tr>
<tr>
<td>Median rPFS (months) (95% CI)</td>
<td>NR (13.8, NR)</td>
<td>3.7 (3.6, 4.6)</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17 (0.14, 0.21)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value is derived from an unstratified log-rank test
<sup>b</sup> Hazard Ratio is derived from an unstratified proportional hazards model. Hazard ratio <1 favors XTANDI NR denotes “not reached”.

Note: As of the cutoff date for the rPFS analysis, 1633 patients had been randomized.

Reference ID: 4001743
Time to initiation of cytotoxic chemotherapy was prolonged after XTANDI treatment, with a median of 28.0 months for patients on the XTANDI arm versus a median of 10.8 months for patients on the placebo arm [HR=0.35 (95% CI: 0.30, 0.40), p < 0.0001].

The median time to first skeletal-related event was 31.1 months for patients on the XTANDI arm versus 31.3 months for patients on the placebo arm [HR = 0.72 (95% CI: 0.61, 0.84), p < 0.0001]. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

**Study 3: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC**

Study 3 was conducted in 375 chemotherapy-naïve patients who were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate to severe pain from prostate cancer were excluded. Patients could have received prior bicalutamide, but those whose disease had progressed on prior antiandrogen therapy (e.g. bicalutamide) were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event), the initiation of subsequent antineoplastic agent, unacceptable toxicity, or withdrawal. Radiographic disease progression was assessed by Independent Central Review (ICR) using the Prostate Cancer Clinical Trials Working Group 2 criteria and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. Radiographic progression-free survival (rPFS) was defined as the time from randomization to the first objective evidence of radiographic progression as assessed by ICR or death, whichever occurred first.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 48-96) and the racial distribution was 93% Caucasian, 5% Black, 1% Asian and 1% Other. The ECOG performance status score was 0 for 74% of patients and 1 for 26% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 58% of patients, and 2-3 (mildly symptomatic) in 36% of patients as defined
by the Brief Pain Inventory Short Form Question 3 (worst pain over past 24 hours at study entry). Ninety-eight percent of patients had objective evidence of disease progression at study entry. Forty-six percent of patients had received prior treatment with bicalutamide while no patients received prior treatment with enzalutamide.

An improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with bicalutamide (Table 7, Figure 6).

Table 7: Radiographic Progression-free Survival of Patients in Study 3

<table>
<thead>
<tr>
<th></th>
<th>XTANDI</th>
<th>Bicalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Progression or Deaths (%)</td>
<td>72 (39%)</td>
<td>74 (39%)</td>
</tr>
<tr>
<td>Median PFS (months) (95% CI)</td>
<td>19.5 (11.8, NR)</td>
<td>13.4 (8.2, 16.4)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60 (0.43, 0.83)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Hazard Ratio is derived from an unstratified proportional hazards model. Hazard ratio <1 favors XTANDI NR denotes “not reached”.

Figure 6. Kaplan-Meier Curves of Radiographic Progression-free Survival in Study 3

16 HOW SUPPLIED/STORAGE AND HANDLING

- XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ. XTANDI capsules are available in the following package sizes:
  - Bottles of 120 capsules (NDC 0469-0125-99)

Recommended storage: Store XTANDI capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).
Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- Inform patients receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their physician right away if they have loss of consciousness or seizure.
- Inform patients to contact their physician right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Apprise patients of the most common side effects associated with XTANDI: 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. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Inform patients that XTANDI may cause infections, falls and fall-related injuries, and hypertension.
- Inform patients that XTANDI can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI. Advise male patients to use a condom if having sex with a pregnant woman [see Use in Specific Populations (8.3)].
**What is XTANDI®?**

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. It is not known if XTANDI is safe and effective in children.

**Who should not take XTANDI?**

XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

**What should I tell my healthcare provider before taking XTANDI?**

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See “Who should not take XTANDI?”
- Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.
- You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.
- Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

**How should I take XTANDI?**

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

**What are the possible side effects of XTANDI?**

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
• **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

**The most common side effects of XTANDI include:**

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store XTANDI?**

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

**Keep XTANDI and all medicines out of the reach of children.**

**General information about XTANDI.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

**What are the ingredients in XTANDI?**

**Active ingredient:** enzalutamide

**Inactive ingredients:** caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide


© 2016 Astellas Pharma US, Inc.

XTANDI® is a registered trademark of Astellas Pharma Inc.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2016