PDL NEW DRUG REVIEW

Proprietary Name: Xtandi®
Common Name: enzalutamide
PDL Category: Antineoplastics-Antiandrogens

Comparable Products	Preferred Drug List Status
Zytiga	Non-Recommended

Indications and Usage: For the treatment of patients with metastatic castration-resistant prostrate cancer who have previously received docetaxel. This is a pregnancy category X medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Capsules; 40mg

Drug Interactions: Concomitant use of CYP2C8 inhibitors with Xtandi® should be avoided if possible; however, if not possible, the dose of Xtandi® should be reduced. Concomitant use of Xtandi® with strong or moderate CYP2C8 inducers (ie rifampin) should also be avoided if possible. Concomitant use of strong and moderate CYP3A4 inducers (ie carbamazepine, phenobarbital, phenytoin, and rifampin) should be avoided if possible. Lastly, Xtandi® is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of Xtandi® with narrow therapeutic index drugs metabolized by CYP3A4 should be avoided; however, if warfarin use cannot be avoided, additional INR monitoring is recommended.

Recommended Dosage: The recommended dose is four-40mg capsules (160mg) given by mouth once daily with or without food. Capsules should not be chewed, dissolved, or opened. If a ≥ Grade 3 toxicity or intolerable side effect is reported, withhold medication for one week or until symptoms improve to ≤ Grade 2. The same or reduced dose may be resumed if warranted. While strong CYP2C8 inhibitors should be avoided with Xtandi®, the dose of Xtandi® should be reduced to 80mg QD if the combination cannot be avoided. Dose adjustment is not needed for those with mild or moderate renal or hepatic impairment; however, use in those with severe renal impairment, end-stage renal disease, or severe hepatic impairment has not been assessed.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most commonly reported adverse events with Xtandi® include asthenic conditions (includes asthenia and fatigue; 6.2%), peripheral edema (2.1%), arthralgia (3.2%), musculoskeletal pain (3.5%), muscular weakness (3%), musculoskeletal stiffness (2.3%), diarrhea (4.3%), hot flush (10%), hypertension (3.6%), headache (6.6%), dizziness (includes dizziness and vertigo; 2%), spinal cord compression & Cauda Equina Syndrome (2.9%), paresthesia (2.1%), mental impairment disorders (includes amnesia, memory impairment, cognitive disorder, and disturbance in attention; 2.5%), hypoesthesia (2.2%), upper respiratory tract infection (4.4%), lower respiratory tract/lung infection (includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection; 3.7%), insomnia (2.8%), anxiety (2.5%), hematuria (2.4%), fall (3.3%), pruritus (2.5%), dry skin (2.2%), and epistaxis (2%).

In clinical trials, 1% of the Xtandi® group died from infections or sepsis as compared with 0.3% of the placebo group. Grade 1-4 neutropenia occurred in 15% of the Xtandi® group vs 6% of the placebo group, while thrombocytopenia was comparable in both arms (0.5% Xtandi® vs 1% placebo). Lastly, 1.6% of the Xtandi® group reported Grade 1 or 2 hallucinations as compared with 0.3% of the placebo group; however, the majority of those having hallucinations were also on opioid-containing medications.

Contraindications: Xtandi® is not indicated for use in women and is contraindicated in women who are or may become pregnant.

Manufacturer: Astellas Pharma US, Inc

Analysis: Enzalutamide, the active ingredient of Xtandi®, is an androgen receptor inhibitor. It acts on different steps of the androgen receptor signaling pathway. It has been shown to competitively inhibit androgen binding to androgen receptors as well as to inhibit androgen receptor nuclear translocation and interaction with DNA. *In vitro*, enzalutamide decreased proliferation and induced cell death of prostate cancer.

One randomized, placebo-controlled study assessed for the safety and efficacy of Xtandi® in those with metastatic castration-resistance prostrate cancer who had received prior therapy with docetaxel (N=1199). The primary outcome was overall survival. Results suggest that there was a statistically significant improvement in overall survival in the Xtandi® arm as compared with placebo. 38.5% of the Xtandi® group died (N=308) as compared with 53.1% (N=212) of the placebo group. The median survival was 18.4 months in the Xtandi® group vs 13.6 months in the placebo group ($p<0.0001$).

There is a warning regarding the risk of seizure with Xtandi® use. In the clinical trial, 0.9% (N=7/800) experienced a seizure as compared to no seizures in the placebo group. The seizures occurred 31-603 days after the start of Xtandi®. Once treatment was discontinued, all seizures resolved. All subjects with history of seizure, brain injury with loss of consciousness, etc were excluded from the trial; thus, the safety of Xtandi® use in this population is not known. Due to the risk of seizure, it is therefore recommended that all patients be educated on the risk of engaging in any activity where loss of consciousness could cause harm to themselves or others.

It is recommended that Xtandi® be added to the Recommended Drug List as a non-recommended drug, as it is not intended as a first-line treatment option.

PDL Placement:
- ☐ **Recommended**
- ☒ **Non-Recommended**

References

[1] Xtandi [package insert]. Northbrook, IL: Astellas Pharma US; 2012.

[2] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *NEJM*. 2012; 367(13): 1187-97.