

# MTF Formulary Management for Prostate Subclass I and II Cancer Drugs

Defense Health Agency Pharmacy Operations Division

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**Bottom-line:**

- The designated BCF agent is Casodex (bicalutamide).
- All the Prostate Cancer Subclass I and II drugs are designated as Uniform Formulary.
- Prior Authorization for Nilandron (nilutamide) was added to reflect FDA indications for this drug. Prior Authorization for Zytiga (abiraterone acetate) and Xtandi (enzalutamide) also reflect the FDA-approved indications.

**Uniform Formulary Decision:** The Director, DHA approved the recommendations from the February 2015 DoD P&T Committee meeting in 5 May 2015, with an implementation date of 19 Aug 2015.

Uniform Formulary (UF) drugs		Non-Formulary (NF) drugs
BCF drugs - MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
Subclass I <ul style="list-style-type: none"> <li>• Casodex (bicalutamide)</li> </ul>	Subclass I <ul style="list-style-type: none"> <li>• Eulexin (flutamide)</li> <li>• Nilandron (nilutamide)**</li> </ul> Subclass II <ul style="list-style-type: none"> <li>• Zytiga (abiraterone acetate)**</li> <li>• Xtandi (enzalutamide)**</li> </ul>	<b>N/A</b> - No Prostate Cancer drugs are designated non-formulary
**Prior authorization criteria apply to Nilandron (nilutamide), Zytiga (abiraterone acetate), and Xtandi (enzalutamide)**; see below.		

## Clinical Summary

### Subclass I (Anti-Androgens)

- All Subclass I agents are indicated for use with additional androgen suppression via medical or surgical castration.
- For Subclass I, bicalutamide is at least as effective as flutamide, based on one head-to-head trial. Bicalutamide is also preferred over flutamide and nilutamide in terms of safety and dosing. Nilutamide is the sole Subclass I agent with an FDA indication for surgical castration.
- In a meta-analysis reviewing flutamide and nilutamide, there was no 2-year survival difference over luteinizing hormone releasing hormone (LHRH) analogue or surgical castration (Lancet 2000). There was a 2.9% increase in overall survival difference at 5 years (0.4% to 5.4% 95% Confidence Interval) for the anti-androgens vs. LHRH analogue or surgical castration.
- Bicalutamide has the convenience of once daily dosing, compared to flutamide's TID dosing and nilutamide's dosing (two tabs daily for 30 days, then once daily thereafter).
- The American Society of Clinical Oncologists/Cancer Care Ontario 2014 Guidelines found limited data regarding clinical benefits of the Subclass I agents. The guidelines stated that anti-androgens demonstrate unknown survival and quality of life benefit.
- Although nilutamide has no compelling advantages compared with flutamide or bicalutamide and has the least favorable safety profile, it is required on the UF due to its unique indication for use in combination with surgical castration.

### Subclass II (Survival Prolonging Drugs)

- The Subclass II agents abiraterone acetate (Zytiga) and enzalutamide (Xtandi) are recent additions to prostate cancer therapeutic armamentarium. Zytiga is a CYP17 enzyme complex inhibitor, while Xtandi is an advanced anti-androgen.
- Both Zytiga and Xtandi have independently been shown to improve overall survival and progression free survival when compared to placebo, both in the post chemotherapy and chemotherapy naïve settings.

- According ASCO/CCO guidelines and National Comprehensive Cancer Network guidelines 2015, both drugs have demonstrated clinical benefit in prostate cancer, irrespective of chemotherapy status. No data informs proper sequencing and some data suggests cross resistance between newer agents when used sequentially.
- Zytiga requires the co-administration of prednisone to help mitigate the mineralocorticoid excess that can result from its mechanism of action. Xtandi does not require steroids, but 30-47% of patients in both phase 3 studies that led to its approval were on some form of steroid therapy during the trials that led to its approval.

## Safety

### Subclass I (Anti-Androgens)

- The prostate Subclass I drugs have mostly similar adverse event profiles to include hot flashes, gynecomastia, and breast pain, particularly when used in conjunction with medical castration.
- Flutamide causes gastrointestinal side effects at a higher rate compared to bicalutamide, based on a head to head study that led to increased withdrawal rate amongst flutamide users.
- Nilutamide has a black box warning for pulmonary toxicity and delays visual light-to-dark adaptation that can limit its use.

### Subclass II (Survival Prolonging Drugs)

- The 2 Subclass II agents have differing safety profiles. Zytiga can cause adrenocortical insufficiency, hypertension, hypokalemia, and edema and requires close monitoring for these complications. Xtandi has had unique issues with seizures as well as hypertension when compared to placebo.

### Overall

- The choice of prostate cancer agent depends on clinical considerations, patient preferences, prior treatment, presence or absence of visceral disease, symptoms and potential side effect profiles.
- All agents in Subclass I and II are required on the UF to meet the needs of the MHS population.

## Prior Authorization Criteria:

**Nilutamide.** PA criteria apply to all new users of nilutamide. Nilutamide is approved if:

- Patient has experienced significant adverse effects or contraindication from bicalutamide or flutamide; or
- Has experienced therapeutic failure with bicalutamide or flutamide; or
- Patient has a diagnosis of metastatic prostate cancer (stage D2) disease and patient has undergone orchiectomy.

**Zytiga and Xtandi:** The previously approved prior authorization criteria for Zytiga and Xtandi were maintained.

## References

- DoD P&T Committee minutes: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.express-scripts.com/tricareformulary>
- Prior Authorization/Medical Necessity forms: See TRICARE Formulary Search Tool above.
- Point of contact for additional information: [usarmy.jbsa.medcom-ameddcs.list.pecuf2@mail.mil](mailto:usarmy.jbsa.medcom-ameddcs.list.pecuf2@mail.mil)

Prostate Cancer Subclass I & II Drugs Price Comparison at MTF	
Drug	MTF cost/month (February 2015)
<b>Basic Core Formulary</b>	
Casodex (bicalutamide)	<b>\$</b> Most Cost-Effective
<b>Uniform Formulary</b>	
Eulexin (flutamide)	<b>\$</b> Cost-Effective
Zytiga (abiraterone acetate)	<b>\$\$</b> Cost-Effective
Xtandi (enzalutamide)	<b>\$\$</b> Cost-Effective
Nilandron (nilutamide)	<b>\$\$\$</b> Less Cost-Effective
Legend: <b>\$</b> = "Most Cost-Effective" Represents Rx's with the <u>lowest cost</u> and best clinical efficacy <b>\$\$</b> = "Less Cost-Effective" Represents <u>higher cost</u> Rx's similar clinical efficacy <b>\$\$\$</b> = "Less Cost-Effective" Represents <u>next higher cost</u> Rx's with similar clinical efficacy <b>\$\$\$\$</b> = "Least Cost-Effective" Represents Rx's with the <u>highest cost</u> with similar clinical efficacy	