Pharmacy Medical Necessity Guidelines: Xtandi® (enzalutamide)

Effective: June 13, 2017

<table>
<thead>
<tr>
<th>Prior Authorization Required</th>
<th>Type of Review – Care Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>√</td>
<td>Type of Review – Clinical Review</td>
</tr>
<tr>
<td>Not Covered</td>
<td>√</td>
</tr>
<tr>
<td>Pharmacy (RX) or Medical (MED) Benefit</td>
<td>RX Department to Review</td>
</tr>
</tbody>
</table>

This Pharmacy Medical Necessity Guideline applies to the following:

Tufts Health Plan Commercial Plans
- Tufts Health Plan Commercial Plans – large group plans
- Tufts Health Plan Commercial Plans – small group and individual plans

Tufts Health Public Plans
- Tufts Health Direct – Health Connector
- Tufts Health Together – A MassHealth Plan
- Tufts Health RITogether – A Rite Care + Rhody Health Partners Plan

Tufts Health Freedom Plan products
- Tufts Health Freedom Plan - large group plans
- Tufts Health Freedom Plan - small group plans

Fax Numbers:
RXUM: 617.673.0988

Note: For Tufts Health Plan Medicare Preferred Members, please refer to the Tufts Health Plan Medicare Preferred Prior Authorization Criteria. Background, applicable product and disclaimer information can be found on the last page.

OVERVIEW
Prostate cancer is the second leading cause of cancer-related death in American men; one in six men will be diagnosed with prostate cancer during their lifetime. Men with prostate cancer may or may not experience symptoms. If symptoms do occur, they may include problems with urination, erectile dysfunction, blood in the urine or semen, and frequent pain in the lower back, hips, or upper thighs. Because these symptoms can closely mimic benign prostatic hyperplasia or other complications of the prostate, noncancerous conditions should be ruled out. Once a diagnosis of prostate cancer is confirmed, the cancer is graded and staged.

Prognosis and treatment selection depend on the grade and stage of the cancer; the patient’s age, experience of symptoms (if any), and presence of comorbidities; risk of cancer spread; whether the cancer is the first occurrence or recurrent; life expectancy; and patient preference. Castration-resistant prostate cancer refers to when men with advanced disease stop responding to traditional androgen deprivation therapy due to reactivated androgen-receptor signaling.

FOOD AND DRUG ADMINISTRATION-APPROVED INDICATIONS
Xtandi (enzalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

COVERAGE GUIDELINES
The plan may authorize coverage of Xtandi (enzalutamide) for Members when all of the following criteria are met:

1. Documented diagnosis of metastatic castration-resistant prostate cancer (mCRPC) AND

2. The prescribing physician is an oncologist or urologist AND

3. Documented failure, contraindication or intolerance to prior treatment with abiraterone (Zytiga®)

Off-label Use Coverage for Other Cancer Diagnoses
Coverage for other cancer diagnoses may be authorized provided effective treatment with such drug is recognized for treatment of such indication in one of the standard reference compendia, or in the medical literature, or by the Massachusetts commissioner of Insurance (commissioner) under the provisions of the “Sullivan Law”: (M.G.L. c.175, s.47K).

The plan may authorize coverage for use for other cancer diagnoses provided effective treatment with such drug is recognized as a “Medically Accepted Indication” according to the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium as indicated by a Category 1 or 2A for quality of evidence and level of consensus.
Note: The plan requires prescribers to submit clinical documentation supporting the drug's effectiveness in treating the intended malignancy, including the applicable NCCN guideline(s).

In cases where the requested off-label use for the diagnosis is not recognized by the NCCN Drugs and Biologics Compendium, the plan will follow the Centers for Medicare and Medicaid Services (CMS) guidance, unless otherwise directed by the commissioner, and accept clinical documentation referenced in one of the other "Standard Reference Compendia" noted below or supported by clinical research that appears in a regular edition of a "Peer-Reviewed Medical Literature" noted below.

"Standard Reference Compendia"
1. American Hospital Formulary Service – Drug Information (AHFS-DI)
2. Thomson Micromedex DrugDex
3. Clinical Pharmacology (Gold Standard)
4. Wolters Kluwer Lexi-Drugs

"Peer Reviewed Medical Literature"
- American Journal of Medicine
- Annals of Internal Medicine
- Annals of Oncology
- Annals of Surgical Oncology
- Biology of Blood and Marrow Transplantation
- Blood
- Bone Marrow Transplantation
- British Journal of Cancer
- British Journal of Hematology
- British Medical Journal
- Cancer
- Clinical Cancer Research
- Drugs
- European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology)
- Gynecologic Oncology
- International Journal of Radiation, Oncology, Biology, and Physics
- The Journal of the American Medical Association
- Journal of Clinical Oncology
- Journal of the National Cancer Institute
- Journal of the National Comprehensive Cancer Network (NCCN)
- Journal of Urology
- Lancet
- Lancet Oncology
- Leukemia
- The New England Journal of Medicine
- Radiation Oncology

When the plan evaluates the evidence in published, peer-reviewed medical literature, consideration will be given to the following:
1. Whether the clinical characteristics of the beneficiary and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients.
4. Whether the study is appropriate to address the clinical question.
   a. whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question (e.g., in some clinical studies it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover);
   b. that non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs; and,
   c. that case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

LIMITATIONS
1. The plan will not authorize the use of Xtandi (enzalutamide) for conditions other than those listed above without appropriate documentation.
2. A quantity limitation of 120 tablets per 30 days applies.

CODES
None

REFERENCES

**APPROVAL HISTORY**
December 10, 2012: Reviewed by Pharmacy & Therapeutics Committee.

Subsequent endorsement date(s) and changes made:
- November 5, 2013: No changes.
- October 7, 2014: Removed the criteria: Documented failure, contraindication or intolerance to prior taxane chemotherapy (i.e., docetaxel, cabazitaxel) due to recent expanded indication in men who have not yet received chemotherapy; and added urologist to the prescribing physicians.
- October 6, 2015: No changes.
- January 1, 2016: Administrative change to rebranded template applicable to Tufts Health Direct.
- June 14, 2016: Removed the criteria "Documented failure, contraindication or intolerance to prior treatment with abiraterone (Zytiga®)" due to recommendations from current treatment guidelines. Added limitation #1 “The plan will not authorize the use of Xtandi (enzalutamide) for conditions other than those listed above without appropriate documentation.” Effective 10/1/16, Medical Necessity Guideline applies to Tufts Health Together.
- September 13, 2016: Added documented failure, contraindication, or intolerance to prior treatment with abiraterone (Zytiga®) to approval criteria.
- April 11, 2017: Administrative update, Adding Tufts Health RITogether to the template.
- June 13, 2017: No changes

**BACKGROUND, PRODUCT AND DISCLAIMER INFORMATION**
Pharmacy Medical Necessity Guidelines have been developed for determining coverage for plan benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. They are used in conjunction with a Member’s benefit document and in coordination with the Member’s physician(s). The plan makes coverage decisions on a case-by-case basis considering the individual Member’s health care needs. Pharmacy Medical Necessity Guidelines are developed for selected therapeutic classes or drugs found to be safe, but proven to be effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. The plan revises and updates Pharmacy Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

This Pharmacy Medical Necessity Guideline does not apply to Uniformed Services Family Health Plan Members or to certain delegated service arrangements. Unless otherwise noted in the Member’s benefit document or applicable Pharmacy Medical Necessity Guideline, Pharmacy Medical Necessity Guidelines do not apply to CareLinkSM Members. For self-insured plans, drug coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a coverage guideline and a self-insured Member’s benefit document, the provisions of the benefit document will govern. Applicable state or federal mandates will take precedence.
For Tufts Health Plan Medicare Preferred, please refer to Tufts Health Plan Medicare Preferred Prior Authorization Criteria.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this policy is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to Member eligibility and benefits on the date of service, coordination of benefits, referral/authorization and utilization management guidelines when applicable, and adherence to plan policies and procedures and claims editing logic.