Introduction

The prostate gland is found only in men and produces some of the fluid that makes up semen. The gland is below the bladder. An enlarged prostate and prostate cancer are two separate conditions. An enlarged prostate is a prostate that simply gets bigger as a man ages. Prostate cancer arises from prostate cells that grow uncontrollably. There are several ways of treating prostate cancer. This policy describes when certain drugs may be covered to treat prostate cancer that doesn’t respond to medication or hormone therapy and has spread to other parts of the body.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Zytiga® (abiraterone)       | Zytiga® (abiraterone) may be considered medically necessary when used in combination with prednisone for the treatment of patients with:  
|                             | • Metastatic castrate-resistant prostate cancer (CRPC)  
|                             | OR  
|                             | • Metastatic high-risk castration-sensitive prostate cancer (CSPC)  
| Yonsa® (abiraterone)        | Yonsa® (abiraterone) may be considered medically necessary when used in combination with methylprednisolone or other corticosteroid for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).  
| Xtandi® (enzalutamide)      | Xtandi® (enzalutamide) may be considered medically necessary for the treatment of patients with:  
|                             | • Castration-resistant prostate cancer (CRPC)  
|                             | OR  
|                             | • Metastatic castration-sensitive prostate cancer (mCSPC)  
|                             | AND  
|                             | • Xtandi® (enzalutamide) is used in combination with androgen deprivation therapy (ADT) as documented by:  
|                             | o Concurrently receiving a gonadotropin-releasing hormone (GnRH) analog  
|                             | OR  
|                             | o Having had bilateral orchiectomy  
| Nubeqa® (darolutamide)      | Nubeqa® (darolutamide) may be considered medically necessary for the treatment of patients with non-metastatic castration-resistant prostate cancer.  
| Erleada™ (apalutamide)      | Erleada™ (apalutamide) may be considered medically necessary for the treatment of patients with:  
|                             | • Metastatic castration-sensitive prostate cancer  
|                             | OR  
|                             | • Non-metastatic castration-resistant prostate cancer  
| Drug                        | Investigational                                                                                                                                 |
| As listed                   | All other uses of the medications listed in this policy are considered investigational. |
Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Drugs listed in policy may be approved up to 3 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy.</td>
</tr>
</tbody>
</table>

Documentation Requirements

The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

N/A

Related Information

Benefit Application

This policy is managed through the Pharmacy benefit.

Evidence Review

Description

Prostate cancer is a neoplastic disease of the prostate gland. Prostate cancer arises from mutations in cells of the prostate that cause overexpression of enzymes that support androgen
biosynthesis, loss of regulation of cell death within the tumor cells, and up regulation of androgen receptors. Androgen receptor binding by androgens plays a crucial role in prostate cancer progression. Most prostate cancers respond to androgen deprivation.

Approximately 60% of all cases of prostate cancer are diagnosed in men 65 years of age or older and 97% occur in men 50 and older. CRPC is a term used to describe prostate cancer which has progressed despite local therapy and first-line hormonal therapy assuring castrate levels of testosterone. Prostate cancers typically progress slowly and there is a high rate of survival for disease detected in early stages, but not for advanced disease stages. In the US, the 5-year survival rate is effectively 100% when the disease is local or regional, but this drops to 31% for disease with distant metastases.

**Disease Burden**

Prostate cancer is the second most common cause of cancer death in American men. In 2013, an estimated 238,590 men are expected to be diagnosed with prostate cancer, and approximately 29,720 are expected to have died from the disease. While it is prevalent, only 15% of all prostate cancer patients develop mCRPC prior to chemotherapy, and just 9% of all prostate cancer patients progress to mCRPC on first-line docetaxel chemotherapy.

The condition is associated with a substantial economic burden, due to high incidence rates and high costs associated with management of advanced cancer stages. The high management cost burden arises from the requirement for hospitalizations, chemotherapy, palliative surgical procedures, and computed tomography (CT) or magnetic resonance imaging (MRI) scans to monitor potential bone metastases. In 2007, per-patient per-month CRPC costs for men over the age of 40 were approximately $1,800, with ambulatory visits ($1,152) and inpatient stays ($559) comprising the majority of these costs. Total all-cause healthcare costs for these same patients totaled $3,500 per-patient per-month.

**Rationale**

**Treatment Alternatives**

Several approved pharmacotherapeutic alternatives for mCRPC have demonstrated some benefit in estimated survival compared with acceptable controls.
**Zytiga® (abiraterone) + prednisone**

Zytiga® (abiraterone) acetate is an oral drug that is converted in vivo to abiraterone a CYP17 complex (17α-hydroxylase/C17,20-lyase) inhibitor that interrupts androgen biosynthesis throughout the body (testes, adrenal gland, and prostate tumor). Prostate cancer is very often an androgen-driven disease. CYP17 inhibition may also lead to increased mineralocorticoid production by the adrenal gland secondary to increased adrenocorticotropic hormone (ACTH) production from a feedback mechanism induced by low cortisol levels. Up regulated ACTH leads to increased deoxycorticosterone which exhibits mineralocorticoid activity. Results from clinical trials have shown that coadministration of a corticosteroid (eg, prednisone) with abiraterone reduces the incidence and severity of mineralocorticoid excess associated adverse reactions. An RCT showed that abiraterone and prednisone improved radiographic progression-free survival, time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration in improvement status.

**Xtandi® (enzalutamide)**

Xtandi® (enzalutamide) is indicated for the treatment of CRPC or mCSPC. The efficacy was demonstrated in five randomized, multicenter clinical trials. All patients received concomitant GnRH therapy or had prior bilateral orchiectomy. One well-designed RCT has shown enzalutamide prolongs overall survival (OS) by 4.8 months, time to prostate-specific antigen (PSA) progression (TTPP), radiographic progression-free survival (rPFS), and time to first skeletal-related event (SRE) compared with placebo. There is currently no direct evidence with which to assess real world comparative effectiveness. Indirect evidence suggests a similar modest (2-5 month) increase in overall survival and hazard for risk of death with enzalutamide, abiraterone, or cabazitaxel in patients with mCRPC previously treated with a docetaxel-based regimen. However, it is important to note that the abiraterone and cabazitaxel studies had control arms which included agents with anti-tumor activity (prednisone and mitoxantrone + prednisone, respectively) compared to placebo control for enzalutamide. The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the Xtandi®-treated patients are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. The most significant warning reported is for seizure, although this occurs rarely (incidence about 0.5%). Indirect evidence suggests favorable safety and tolerability compared to other second-line treatments with survival benefit for mCRPC. Enzalutamide lacks the detrimental effects of mineralocorticoid excess induced by Xtandi® (enzalutamide), and thus does not require co-administration with corticosteroids, which may complicate CRPC treatment. Unlike Jevtana®
(cabazitaxel), Xtandi® (enzalutamide) is not reported to commonly cause neuropathy or severe myelosuppression, two significant toxicities which can lead to morbidity and limit additional therapy in this patient population.

Guideline Recommendations

The latest prostate cancer guidelines from the NCCN recommend the following systemic therapies for advanced disease (primarily category 2a unless otherwise labeled):

Metastatic castration-recurrent prostate cancer

Asymptomatic visceral disease: Sipuleucel-T or secondary hormone therapy (including abiraterone or enzalutamide) or docetaxel or clinical trial

Bone metastases: Denosumab (1) or zoledronic acid (1)

Disease recurrence post-abiraterone or enzalutamide or intolerance: Docetaxel (1) or abiraterone or enzalutamide or Radium-223 for symptomatic bone metastases (1) or Sipuleucel-T* or other secondary hormone therapy or clinical trial.

Disease recurrence post-docetaxel or first-line therapy intolerance: Abiraterone (1, post-docetaxel) or enzalutamide (1, post-docetaxel) or cabazitaxel (1, post-docetaxel) or salvage chemotherapy or docetaxel rechallenge or mitoxantrone or other secondary hormone therapy or Provenge® (sipuleucel-T)* or clinical trial

*Note: Provenge® (sipuleucel-T) is recommended only for asymptomatic or minimally symptomatic patients with an ECOG performance status of 0-1. It is not indicated for patients with hepatic metastases or life expectancy <6 months.

General: Maintain castrate serum testosterone levels

Symptomatic visceral disease: Docetaxel or mitoxantrone (for patients not candidates for docetaxel) or abiraterone or enzalutamide or palliative care for symptomatic bone metastases or clinical trial

These guidelines are generally aligned with evidence-based European guidelines, excepting the adoption of use of Xtandi® (enzalutamide).
Non-Metastatic castration-resistant prostate cancer

NCCN guidelines recommend apalutamide or enzalutamide, especially if PSA doubling time is ≤ 10 months. Additionally, bone support should be used in patients receiving this medication (fracture 11% vs 6.5% placebo).

National Comprehensive Cancer Network (NCCN) Compendium

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium is based directly on the NCCN Clinical Practice Guidelines in Oncology. The compendium lists specific panel recommendations for off-label uses of drugs, and each recommendation is supported by a level of evidence category.

The NCCN Categories of Evidence and Consensus used in the recommendations are:

- Category 1: The recommendation is based on high level evidence (eg, randomized controlled trials) and there is uniform NCCN consensus.
- Category 2A: The recommendation is based on lower level evidence and there is uniform NCCN consensus.
- Category 2B: The recommendation is based on lower level evidence and there is nonuniform NCCN consensus (but no major disagreement).
- Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

2014 Update

A search of the literature from 7/1/13 to 10/31/14 did not identify new evidence requiring changes to this policy.

2015 Update

Updated new indications and NCCN recommendations for Xtandi® (enzalutamide). A search of the literature from 7/1/14 to 8/31/15 did not identify new evidence requiring changes to this policy.
2016 Update

Updated policy based on new NCCN recommendations. Zytiga® (abiraterone acetate) step removed for Xtandi® (enzalutamide).

2018 Update

Updated new product labeling and NCCN recommendations which now include Erleada™. A search of the literature from 4/11/2017 to 3/13/2018 did not identify new evidence requiring changes to this policy. Yonsa® (abiraterone) criteria was added.

2019 Update

Reviewed prescribing information for all drugs and updated Erleada® (apalutamide) coverage criteria adding coverage for the treatment of patients with metastatic castration-sensitive prostate cancer. No new evidence was identified that would require changes to other drugs listed in this policy. Added coverage criteria for a new drug Nubeqa® (darolutamide).

References


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### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/09/13</td>
<td>New policy effective May 1, 2013. Add to Prescription Drug Section. Enzalutamide (Xtandi®) is approved for the treatment of prostate cancer when conditions are met.</td>
</tr>
<tr>
<td>07/08/13</td>
<td>Minor Update – Clarification was added to the policy that it is managed through the member’s pharmacy benefit; this is now listed in the header and within the coding section.</td>
</tr>
<tr>
<td>12/04/13</td>
<td>Replace policy. Policy section updated with the addition of abiraterone (Zytiga®), considered medically necessary for treating castration-resistant prostate cancer in combination with prednisone. (This was previously addressed in policy 5.01.540.) Rationale section updated in support of this addition.</td>
</tr>
<tr>
<td>12/08/14</td>
<td>Annual review. Policy updated with literature review; no change in policy statements</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Updated enzalutamide (Xtandi®) for new indications.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Interim Update. Medical necessity coverage criteria for enzalutamide (Xtandi®) expanded.</td>
</tr>
<tr>
<td>10/25/16</td>
<td>Minor formatting update. Added second level bullet, Policy section under Enzalutamide (Xtandi®) criteria.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Annual Review, changes approved December 13, 2016. Updated enzalutamide and abiraterone acetate for new indications. Medical necessity coverage criteria updated (Zytiga® step removed).</td>
</tr>
<tr>
<td>05/01/17</td>
<td>Annual Review, changes approved April 11, 2017. A statement outlining the length of</td>
</tr>
</tbody>
</table>
therapy for initial and subsequent approval has been added to the policy.


03/01/18 Interim Review, approved February 27, 2018. Added FDA approved Erleada to policy. Zytiga criteria was revised to include new FDA label update.

07/01/18 Annual Review, approved June 22, 2018. Literature review 04/11/2017 to 3/13/2018. NCCN guidelines updated. Yonsa® (abiraterone) criteria was added to policy.

11/01/18 Interim Review, approved October 26, 2018. Updated Yonsa indication to allow any corticosteroid. Updated Xtandi indication per label.


03/01/20 Interim Review, approved February 20, 2020. Added to Xtandi (enzalutamide) coverage criteria for the treatment of metastatic castration-sensitive prostate cancer.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


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You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

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U.S. Department of Health and Human Services
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Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Ligue para 800-722-1471 (TTY: 800-842-5357)