Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO081

Description

Darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are orally administered androgen receptor inhibitors. Abiraterone (Zytiga, Yonsa) is an androgen biosynthesis inhibitor of CYP17.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
darolutamide (Nubeqa)	300 mg tablets	Prostate cancer, non-metastatic, castration resistant	120 tablets/30 days
apalutamide (Erleada)	60 mg tablets	Prostate cancer, non-metastatic, castration resistant Prostate cancer, metastatic, castration-sensitive	
enzalutamide (Xtandi)	40 mg capsules	Prostate cancer, castration resistant Prostate cancer, metastatic, castration-sensitive	120 capsules/30 days
abiraterone (Yonsa)	125 mg tablets	Prostate cancer, metastatic, castration-resistant, in combination with methyprednisolone	120 tablets/30 days
abiraterone (generic Zytiga)	250 mg tablets	Prostate cancer, metastatic, castration-resistant, in combination with prednisone Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	120 tablets/30 days
abiraterone (Zytiga)	250 mg tablets		
	500 mg tablets		60 tablets/30 days

Initial Evaluation

I. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. The member has **not** previously progressed on darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi) OR abiraterone (Zytiga, Yonsa); **AND**
   D. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi) or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of hormone suppressive therapy outlined below; **AND**
   E. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
   F. A diagnosis of one of the following:
      1. **Non-metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
         i. The member has a PSA-doubling time of 10 months or less during continuous androgen-deprivation therapy or after bilateral orchiectomy; **AND**
         ii. One of the following is prescribed: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
      2. **Metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
         i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
         ii. The request is for brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**
            a. The member has an intolerance or contraindication to generic abiraterone; **OR**
         iii. The request is for enzalutamide (Xtandi); **AND**
            a. The member has an intolerance or contraindication to generic abiraterone or prednisone; **OR**
      3. **Metastatic castration sensitive or castration naïve prostate cancer; AND**
         i. For generic abiraterone:
            a. The member has at least TWO of the following risk factors:
               i. Gleason Score ≥ 7
               ii. Bone lesions

iii. Presence of measurable visceral metastases; **AND**

b. Will be used in combination with prednisone; **OR**

ii. For BRAND abiraterone (Zytiga), apalutamide (Erleada), or enzalutamide (Xtandi):

a. The member has at least TWO of the following risk factors:
   i. Gleason Score ≥ 7
   ii. Bone lesions
   iii. Presence of measurable visceral metastases; **AND**
b. The member must have had inadequate response, intolerance, or contraindication to generic abiraterone; **AND**
c. If the request is for abiraterone (Zytiga), will be used in combination with prednisone

II. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), and abiraterone (Zytiga, Yonsa) are considered investigational when used for all other conditions, including but not limited to:
   A. Cushing's Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by or in consultation with an oncologist or urologist; **AND**
IV. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi) or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of hormone suppressive therapy outlined below; **AND**
V. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
VI. The member has experienced a response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
   1. **Non-metastatic castration resistant prostate cancer;**
      i. The request is for one of the following: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**

2. **Metastatic castration resistant prostate cancer;**
    i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
    ii. The request is for brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**
        a. The member has an intolerance or contraindication to generic abiraterone; **OR**
    iii. The request is for enzalutamide (Xtandi); **OR**
3. **Metastatic castration sensitive prostate cancer;**
    i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
    ii. The request is for enzalutamide (Xtandi) or apalutamide (Erleada); **OR**
    iii. The request is for brand abiraterone (Zytiga); **AND**
        a. The member has had inadequate response, intolerance, or contraindication to generic abiraterone; **AND**
        b. Will be used in combination with prednisone

Supporting Evidence

I. Prostate cancer therapies have been evaluated for safety and efficacy in adults. There are multiple treatment modalities with the direction of therapy depending on the manifestations of the disease. The initial and continued approach should be directed by a specialist due to the nuances of treatment, monitoring of disease, treatment safety, evaluation of efficacy, and consideration for patient specific goals.

II. Many treatment options exist and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited to, radiation therapy, prostatectomy, androgen deprivation pharmacotherapy, bilateral orchiectomy, chemotherapy, abiraterone (Zytiga, Yonsa) or androgen receptor inhibitors (e.g., enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada)). Multi-modal therapy, such as abiraterone or enzalutamide with ADT, is commonly utilized; however, abiraterone and/or androgen receptor inhibitor combinations have not been evaluated for safety and efficacy to date. Continuation of ADT is commonly employed and is recommended as concomitant therapy as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression.

III. Use of androgen receptor inhibitor (e.g., darolutamide [Nubeqa], apalutamide [Erleada], enzalutamide [Xtandi]) therapy after disease progression on abiraterone, or vice versa (i.e., abiraterone/androgen receptor inhibitor crossover therapy), has not yet been evaluated for safety and efficacy in quality clinical trials. One retrospective trial evaluating enzalutamide after treatment with abiraterone showed that very few patients (10% or less) had a significant decrease in PSA with enzalutamide therapy. A retrospective case series showed a similar lack of

efficacy in regards to abiraterone after enzalutamide (Xtandi). Additionally, there are studies to suggest cross resistance between the two therapies.

IV. Non-metastatic castration resistant prostate cancer: darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are the androgen receptor inhibitors that have been evaluated in this stage of disease. Concurrent treatment with steroids is not required. Patients in the trials for each of these medications had a prostate-specific antigen doubling time of 10 months or less, and received GnRH therapy concurrently. Each therapy was evaluated in a double-blind, placebo-controlled trial.
   - Darolutamide (Nubeqa) was evaluated in the ARAMIS TRIAL. The primary outcome, metastasis free survival (MFS), showed a statistical significance over placebo (40 vs 18 months, $p<0.001$). Apalutamide (Erleada) was evaluated in the SPARTAN trial, MFS was statistically significant compared to placebo (40 vs 16 months), and enzalutamide (Xtandi) was evaluated in the PROSPER trial. The MFS was significant compared to placebo (37 months vs 15 months).
   - Darolutamide (Nubeqa) does not cross the blood brain barrier; thus, may offer an improved safety profile compared to enzalutamide and even apalutamide (Erleada). There were low rates of fatigue, falls, fractures, and seizures; however, head-to-head trials have not yet been conducted and caution should be used when comparing across trials to make treatment decisions.

V. Metastatic, castration resistant prostate cancer: enzalutamide (Xtandi) and abiraterone (Zytiga, Yonsa) have been evaluated for safety and efficacy. Enzalutamide (Xtandi) versus placebo was evaluated in those that had previously been treated with chemotherapy and those that were chemotherapy naïve. Overall survival was prolonged in both settings. Abiraterone (Zytiga, Yonsa) plus prednisone has also shown prolonged survival in this setting in those that have been previously treated with chemotherapy and those chemotherapy naïve. Head-to-head trials have not been completed to provide insight to superior therapy between abiraterone (Zytiga, Yonsa) and enzalutamide (Xtandi). Abiraterone (Zytiga, Yonsa) is indicated in combination with prednisone; however, enzalutamide has safety concerns including CNS toxicities and seizures. Additionally, abiraterone (Zytiga, Yonsa) has generic availability.

VI. Metastatic high-risk castration sensitive prostate cancer: abiraterone (Zytiga, Yonsa) plus prednisone has been evaluated for safety and efficacy. High risk disease was defined as having at least two of the following three risk factors: Gleason score eight or greater, presence of three or more bone lesions, evidence of measurable visceral metastases. Overall survival over placebo was shown to be statistically significant for abiraterone (Zytiga, Yonsa).

VII. Apalutamide (Erleada) was evaluated in the metastatic, castration sensitive prostate cancer setting in combination with ADT versus ADT alone. This was not specifically in high risk disease; however, 93% of subjects had a Gleason Score of seven or greater, and all subjects had bone metastases. Fifty-five percent of subjects had bone only metastases, and the remaining had additional metastases. Primary outcomes were radiographic progression free survival, which

were statistically and clinically significant favoring apalutamide (Erleada). Head-to-head trials against abiraterone (Zytiga) have not occurred in this setting; however, the safety profile of abiraterone is further established at this time.

VIII. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADE versus ADT alone. This study was not specifically in high risk disease, however, the majority of subjects (> 67%) had a Gleason score of 8 or greater – nearly 85% had bone metastases or bone and other metastases. Progression-free survival was 19 months for placebo plus ADT and was not reached for enzalutamide (Xtandi). Radiographic progression was experienced by 13.8% of those receiving enzalutamide (Xtandi) and 32.6% for placebo plus ADT. Head-to-head trials against abiraterone have not occurred in this setting; however, abiraterone provides a better value for the treatment of mCSPC at this time. Additionally, enzalutamide (Xtandi) was evaluated in a Phase III open-label trial in addition to ADT versus ADE alone in those that were castration naïve. The primary endpoint of OS was statistically significant in a group of 125 subjects (HR for death: 0.67, CI 0.52-0.86, p=0.002).

Investigational or Not Medically Necessary Uses

I. Therapies in this policy are being evaluated in other conditions; however, quality data indicating safety and efficacy in the following settings are not yet available:
   A. Cushing's Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine cancer

References

1. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-1246.
2. National Comprehensive Cancer Network clinical practice guidelines, prostate cancer. Version 4.2019. Updated August 19, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 8, 2019.
3. El-amm J, Aragon-ching JB. The Current Landscape of Treatment in Non-Metastatic Castration-Resistant Prostate Cancer. Clin Med Insights Oncol. 2019;13:1179554919833927.
4. Nubeqa [Package Insert]. 2019. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.
5. Xtandi [Prescribing Information]. 2019. Astellas Pharma US, Inc. Northbrook, IL, Pfizer Inc. New York, NY.
6. Erleada [Prescribing Information]. 2019. Janssen Pharmaceuticals Companies. Horsham, PA.
7. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol. 2013;24(7):1802-7.
8. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol. 2013;24(7):1807-12.
9. Bianchini D, Lorente D, Rodriguez-vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer. 2014;50(1):78-84.

10. Smith MR, Saad F, Rathkopf DE, et al. Clinical Outcomes from Androgen Signaling-directed Therapy after Treatment with Abiraterone Acetate and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol. 2017;72(1):10-13.
11. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-1418.
12. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474.
13. Yonsa [Package Insert]. 2011. Sun Pharmaceuticals Industries, Inc. Canbury, NJ.
14. Chi KN., Agarwal N., Bjartell A., et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381(1):13-24.
15. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-2986.
16. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-131.

Policy Implementation/Update:

Date Created	September 2011, February 2013, April 2018
Date Effective	September 2011, February 2013, April 2018
Last Updated	December 2019
Last Reviewed	10/2014, 02/2016, 08/2017, 12/2019, 08/2019, 12/2019

Action and Summary of Changes	Date
Addition of enzalutamide (Xtandi) for castration sensitive prostate cancer given new FDA-approved indication. Removal of requirement upon renewal to change to generic abiraterone. Consolidation of requirements for agents in the setting of castration sensitive prostate cancer to streamline policy. Formatting updates	12/2019
Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.	08/2019
Generic abiraterone requirement added prior to use of branded 250 mg.	12/2018
Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.	08/2018
Apalutamide (Erleada) criteria created	04/2018
Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.	02/2018
Enzalutamide (Xtandi) criteria created	02/2013

Abiraterone (Zytiga) criteria created	09/2011