Second Generation Anti-Androgen Agents

EOCCO POLICY

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	Indication	Dosage Form	Quantity Limit
darolutamide (Nubeqa)	Prostate cancer, non-metastatic, castration resistant Prostate cancer, metastatic, castration-sensitive	300 mg tablets	120 tablets/30 days
apalutamide (Erleada)	Prostate cancer, non-metastatic, castration resistant Prostate cancer, metastatic, castration-sensitive	60 mg tablets	
enzalutamide (Xtandi)	Prostate cancer, castration resistant Prostate cancer, metastatic, castration-sensitive	40 mg capsules	120 capsules/30 days
		40 mg tablets	120 tablets/30 days
		80 mg tablets	60 tablets/30 days
abiraterone (Yonsa)	Prostate cancer, metastatic, castration-resistant, in combination with methylprednisolone	125 mg tablets	120 tablets/30 days
abiraterone (generic Zytiga)	Prostate cancer, metastatic, castration-resistant, in combination with prednisone	250 mg tablets	120 tablets/30 days
		500 mg tablets	60 tablets/30 days
abiraterone (Zytiga)	Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	250 mg tablets	120 tablets/30 days
		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 therapies outlined below (e.g., hormone suppression therapy, docetaxel for mCSPC); **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 generic abiraterone 500 mg tablets; **AND**
            a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
         iii. The request is for brand abiraterone (Zytiga), brand abiraterone (Yonsa), or enzalutamide (Xtandi); **AND**
            a. Documentation of intolerance or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); **AND**
            b. If the request is for abiraterone (Zytiga) or abiraterone (Yonsa), will be used in combination with 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 (Grade Group ≥ 2)
            ii. Bone lesions
            iii. Presence of measurable visceral metastases; **AND**
        b. Abiraterone will be used in combination with prednisone; **AND**
            i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **AND**
        c. The request is for generic abiraterone 250 mg tablets; **OR**
            i. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
    ii. **For BRAND abiraterone (Zytiga), apalutamide (Erleada), darolutamide (Nubeqa), or enzalutamide (Xtandi):**
        a. The member has at least TWO of the following risk factors:
            i. Gleason Score ≥ 7 (Grade Group ≥ 2)
            ii. Bone lesions
            iii. Presence of measurable visceral metastases; **AND**
        b. The member must have had an inadequate response, intolerance, or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); **AND**
        c. If the request is for abiraterone (Zytiga), it will be used in combination with prednisone; **AND**
            i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **OR**
        d. If the request is for darolutamide (Nubeqa), it will be used in combination with docetaxel

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 or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, 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 docetaxel for mCSPC; **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 generic abiraterone 500 mg tablets; **AND**
            a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
        iii. 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 (use of 250 mg tablets required); **OR**
        iv. 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**
            a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
        ii. The request is for enzalutamide (Xtandi), darolutamide (Nubeqa), 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 (use of 250 mg tablets required); **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).

- NCCN prostate cancer guidelines provide a category 1 recommendation for use of abiraterone acetate in combination with docetaxel and ADT in those with a high-volume metastatic burden who are candidates for chemotherapy. This is based on the findings from the PEACE-1 clinical trial, which evaluated the safety and efficacy of standard of care (SOC) therapy, defined as docetaxel and ADT, against SOC plus abiraterone acetate and prednisone. The co-primary endpoint consisted of radiographic progression free survival (rPFS) and overall survival (OS). The abiraterone group demonstrated statisitically significant benefit in rPFS and OS with a hazard ratio (HR) was 0.50 (99.9% CI 0.34-0.71; p<0.0001) and 0.75 (95.1% CI 0.59-0.95; p=0.017), respectively. However, further analysis based on volume of metastatic burden revelated that OS was only statistically significant in the population with high-volume metastatic burden (HR 0.72 [95.1% CI 0.55-0.95]; p=0.019) compared to low-volume metastatic burden (HR 0.83 [95.1% CI 0.50-1.39]; p=0.66). According to NCCN, high-volume disease is differentiated from low-volume disease by visceral metastases and/or foru or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. While the addition of docetaxel

to abiraterone acetate and ADT did increase overall incidence of adverse reactions, it did not increase the incidence of severe or fatal adverse events and the safety profile is largely the same.Docetaxel is intended to be used at the same time or within a few weeks of starting therapy with darolutamide or abiraterone. In mHSPC, docetaxel is dosed on every 3 week cycles for a total of 6 cycles; completion of docetaxel therapy should reasonably be able to occur within the initial approval period of 6 months.

VII. Although both strengths (250 mg and 500 mg) of abiraterone (Zytiga) are available in generic formulations, the 500 mg tablet remains at a significantly higher cost (40x greater) than the 250 mg tablet. Thus, use of generic abiraterone 250 mg is required over abiraterone 500 mg tablet.

VIII. 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.

IX. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT 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).

X. Darolutamide (Nubeqa) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT and docetaxel versus ADT/docetaxel alone. This was not specifically in high risk disease; however, the majority of subjects (>77%) had a Gleason score of 8 or greater – nearly 80% had bone metastases and all other subjects had visceral or non-regional lymph node metastases. The hazard ratio for death was 0.68 (95% CI, 0.57 – 0.80; p<0.001) with overall survival (OS) at four years reported as 62.7% in the darolutamide group compared to 50.4% in the placebo group, despite a high percentage of patients who received subsequent life-prolonging systemic therapies (primarily a different androgen-recetpro pathway inhibitor) among those who entered the follow-up in the placebo grup (374 of 495 patients (75.6%). The side effect profile of darolutamide (Nubeqa) was consistent with previous evaluation and a

higher incidence of treatment related adverse events was higher during the period when patients received both docetaxel and darolutamide (Nubeqa), and progressively decreased thereafter.

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

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of darolutamide (Nubeqa) for metastatic castration-sensitive prostate cancer given new FDA-approved indication; Addition of docetaxel in combination with abiraterone acetate for metastatic castration-sensitive prostate cancer with high volume metastatic burden based on category 1 NCCN recommendation; Changed name of policy to 'Second Generation Anti Androgen Agents'	10/2022
Require clinical rationale for use of generic abiraterone 500 mg instead of generic 250 mg	05/2022
Addition of Grade Group referenced with Gleason Score	05/2021
Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets	11/2020
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