

# Antiandrogens (Oral) – apalutamide, darolutamide, enzalutamide

Medical policy no. 21.40.24-1

Effective Date: TBD

## Related medical policies:

Policy Name	Indications
Androgen Biosynthesis Inhibitor	Prostate Cancer

*Note: New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.*

To see the list of the current Apple Health Preferred Drug List (AHPDL), please visit: <https://www.hca.wa.gov/assets/billers-and-providers/apple-health-preferred-drug-list.xlsx>

## Medical necessity

Drug	Medical Necessity
Apalutamide (Erleada) Darolutamide (Nubeqa) Enzalutamide (Xtandi)	<b>Antiandrogens (Oral)</b> may be considered medically necessary in patients who meet the criteria described in the clinical policy below.  If all criteria are not met, the clinical reviewer may determine there is a medically necessary need and approve on a case-by-case basis. The clinical reviewer may choose to use the reauthorization criteria when a patient has been previously established on therapy and is new to Apple Health.

## Clinical policy:

Clinical Criteria	
<b>Non-metastatic castration-resistant prostate cancer (nmCRPC)</b> apalutamide (Erleada) darolutamide (Nubeqa)	Apalutamide (Erleada), darolutamide (Nubeqa), enzalutamide (Xtandi) may be approved when all the following documented criteria are met: <ol style="list-style-type: none"> <li>1. Patient is 18 years of age or older, <b>AND</b></li> <li>2. Prescribed by or in consultation with an oncologist or urologist; <b>AND</b></li> <li>3. Patient must meet one of the following:                             <ol style="list-style-type: none"> <li>a. Patient has either had a bilateral orchiectomy; <b>OR</b></li> <li>b. Patient will use hormone suppression (e.g., GnRH therapy) concurrently; <b>AND</b></li> </ol> </li> <li>4. Diagnosis of one of the following:                             <ol style="list-style-type: none"> <li>a. Non-metastatic castration resistant prostate cancer; <b>OR</b></li> </ol> </li> </ol>
<b>Non-metastatic, castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis</b> enzalutamide (Xtandi)	

	<p>b. Non-metastatic castration sensitive prostate cancer; <b>AND</b></p> <p>5. The patient is in the high-risk or very high-risk group defined by the following:</p> <ul style="list-style-type: none"> <li>a. The patient is node positive; <b>OR</b></li> <li>b. The patient is node negative and has at least TWO of the following risk factors: <ul style="list-style-type: none"> <li>i. Gleason Score <math>\geq 8</math></li> <li>ii. Tumor stage T3 or T4</li> <li>iii. Prostate-specific antigen (PSA) concentration <math>\geq 40</math> ng/mL; <b>OR</b></li> </ul> </li> <li>c. Experienced prostate-specific antigen (PSA) doubling time of <math>&lt;6</math> months or PSA <math>\geq 20</math> ng/mL on androgen deprivation therapy (e.g. GnRH analogs).</li> </ul> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p> <p><b>Criteria (Reauthorization)</b></p> <p>Apalutamide (Erleada), darolutamide (Nubeqa), enzalutamide (Xtandi) may be approved when all the following criteria are met:</p> <ul style="list-style-type: none"> <li>1. Documentation is submitted demonstrating disease stability or a positive clinical response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression).</li> </ul> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p>
<p><b>Castration-resistant prostate cancer</b> Enzalutamide (Xtandi)</p>	<p>Enzalutamide (Xtandi) may be approved when all the following criteria are met:</p> <ul style="list-style-type: none"> <li>1. Patient is 18 years of age or older, <b>AND</b></li> <li>2. Prescribed by, or in consultation with, an oncologist or urologist; <b>AND</b></li> <li>3. Patient must meet one of the following: <ul style="list-style-type: none"> <li>a. Patient has either had a bilateral orchiectomy; <b>OR</b></li> <li>b. Patient will use hormone suppression (e.g., GnRH therapy) concurrently; <b>AND</b></li> </ul> </li> <li>4. Diagnosis of castration resistant prostate cancer; <b>AND</b></li> <li>5. Medication will be used as monotherapy; <b>OR</b></li> <li>6. If the request is for use in setting of HRR mutation, enzalutamide (Xtandi) will be used in combination with talazoparib (Talzenna); <b>AND</b></li> <li>7. Treatment with abiraterone has been ineffective unless it is contraindicated or not tolerated.</li> </ul> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p> <p><b>Criteria (Reauthorization)</b></p>

	<p>Enzalutamide (Xtandi) may be approved when all the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Documentation is submitted demonstrating disease stability or a positive clinical response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression).</li> </ol> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p>
<p><b>Metastatic castration-sensitive prostate cancer</b> apalutamide (Erleada) enzalutamide (Xtandi)</p> <p><b>Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel</b> darolutamide (Nubeqa)</p>	<p>Apalutamide (Erleada), darolutamide (Nubeqa), enzalutamide (Xtandi) may be approved when all the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Patient is 18 years of age or older, <b>AND</b></li> <li>2. Prescribed by, or in consultation with, an oncologist or urologist; <b>AND</b></li> <li>3. Patient must meet one of the following:             <ol style="list-style-type: none"> <li>a. Patient has either had a bilateral orchiectomy; <b>OR</b></li> <li>b. Patient will use hormone suppression (e.g., GnRH therapy) concurrently; <b>AND</b></li> </ol> </li> <li>4. Diagnosis of one of the following:             <ol style="list-style-type: none"> <li>a. Metastatic castration sensitive prostate cancer; <b>OR</b></li> <li>b. Metastatic hormone sensitive prostate cancer; <b>AND</b></li> </ol> </li> <li>5. The patient has at least <u>TWO</u> of the following risk factors:             <ol style="list-style-type: none"> <li>a. Gleason Score <math>\geq 7</math> (Grade Group <math>\geq 2</math>)</li> <li>b. Bone lesions</li> <li>c. Presence of measurable visceral metastases; <b>AND</b></li> </ol> </li> <li>6. Treatment with abiraterone has been ineffective unless it is contraindicated or not tolerated; <b>AND</b></li> <li>7. If the request is for darolutamide (Nubeqa), it will be used in combination with docetaxel</li> </ol> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p> <p><b>Criteria (Reauthorization)</b></p> <p>Apalutamide (Erleada), darolutamide (Nubeqa), enzalutamide (Xtandi) may be approved when all the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Criteria #4 above continues to be met; <b>AND</b></li> <li>2. Documentation is submitted demonstrating disease stability or a positive clinical response to therapy [e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression].</li> </ol> <p>If ALL criteria are met, the request will be authorized for <b>6 months</b>.</p>

## Dosage and quantity limits

Drug	Indication	FDA Approved Dosing	Dosage Form and Quantity Limit
<b>Erleada</b>	Metastatic castration-sensitive prostate cancer	240 mg once daily	<ul style="list-style-type: none"> <li>60 mg tablets: 4 tablets per day</li> <li>240 mg tablets: 1 tablet per day</li> </ul>
	Non-metastatic castration-resistant prostate cancer (nmCRPC)		
<b>Nubeqa</b>	Non-metastatic castration-resistant prostate cancer (nmCRPC)	600 mg (two 300 mg tablets) twice daily	<ul style="list-style-type: none"> <li>300 mg tablets: 4 tablets per day</li> </ul>
	Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel		
<b>Xtandi</b>	Castration-resistant prostate cancer	160 mg once daily	<ul style="list-style-type: none"> <li>40 mg capsules: 4 capsules per day</li> <li>40 mg tablets: 4 tablets per day</li> <li>80 mg tablets: 2 tablet per day</li> </ul>
	Metastatic castration-sensitive prostate cancer		
	Non-metastatic, castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis		

### Coding:

HCPCS Code	Description
<HCPCS Code>	N/A

### Background:

Prostate cancer is amongst the most common cancers in males worldwide. In the United States, 11 percent of males are diagnosed with prostate cancer over their lifetime, with the incidence generally rising with age. There are an estimated 268,490 cases and 34,500 deaths annually. Androgen deprivation therapy (ADT) with or without an androgen receptor pathway inhibitor is a usual first-line option for males with advanced prostate cancer. Many treatment options exist and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited [National Comprehensive Cancer Network Prostate Cancer guideline](#) recommended 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 outside of therapies listed in the

policy. Continuation of ADT is commonly employed and is recommended as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression. Second generation anti-androgen agents act by competitively inhibiting androgen binding to androgen receptors.

## 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 4.2023. Updated September 7, 2023. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).
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]. 2022. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.
5. Xtandi [Prescribing Information]. September 2020. 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. Lortot 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.
17. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in metastatic hormone-sensitive prostate cancer. *N Engl Med* 2022;386:1132-42.
18. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447-460.

19. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. *Nat Rev Urol.* 2017;14(7):415-439.
20. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Jun 2]. *Lancet.* 2023;S0140-6736(23)01055-3. doi:10.1016/S0140-6736(23)01055-3
21. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. *NEJM Evid.* 2022;1(9). doi:10.1056/EVIDoa2200043

## History

Approved Date	Effective Date	Version	Action and Summary of Changes
TBD	TBD	21.40.24-1	Pending Approval (draft/unpublished version) - New policy created

## Oncology Agents: Antiandrogens- Oral

Please provide the information below, please print your answer, attach supporting documentation, sign, date, and return to our office as soon as possible to expedite this request. **Without this information, we may deny the request in seven (7) working days.**

Date of request:	Reference #:	MAS:	
Patient	Date of birth	ProviderOne ID	
Pharmacy name	Pharmacy NPI	Telephone number	Fax number
Prescriber	Prescriber NPI	Telephone number	Fax number
Medication and strength		Directions for use	Qty/Days supply

- Is this request for a continuation of existing therapy?  Yes  No  
If yes, is there documentation demonstrating disease stability or a positive clinical response (e.g., decrease in tumor size or tumor spread, lack of disease progression)?  
 Yes  No
- Is this prescribed by, or in consultation with, any of the following? Check all that apply:  
 Oncologist  Urologist  
 Other. Specify: \_\_\_\_\_
- Has patient had a bilateral orchiectomy?  Yes  No
- Will patient use hormone suppression (e.g., GnRH therapy) with the requested medication?  
 Yes  No
- Indicate patient's diagnosis and answer the associated questions as indicated:  
 Castration-resistant prostate cancer (questions 6 - 8)  
 Metastatic castration-sensitive prostate cancer (questions 9 - 11)  
 Metastatic hormone-sensitive prostate cancer (questions 9 - 11)  
 Non-metastatic castration-resistant prostate cancer (question 12)  
 Non-metastatic castration-sensitive prostate cancer (question 12)  
 Other. Specify: \_\_\_\_\_

### For diagnosis of Castration-resistant prostate cancer:

- Will the requested medication be used as monotherapy?  Yes  No
- Has an HRR gene mutation been confirmed for patient?  Yes  No  
If yes, will the request be used in combination with talazoparib (Talzenna)?  Yes  No
- Has patient had treatment with abiraterone that was ineffective, not tolerated or contraindicated?  
 Yes  No

**For diagnosis of metastatic castration-sensitive or hormone-sensitive prostate cancer:**

9. Does patient have any of the following risk factors? Check all that apply:
- Gleason Score  $\geq 7$  (Grade Group  $\geq 2$ )
  - Bone lesions
  - Presence of measurable visceral metastases
10. Has patient had treatment with abiraterone that was ineffective, not tolerated or contraindicated?  
 Yes    No
11. **If the request is for darolutamide (Nubeqa),** will it be used in combination with docetaxel?  
 Yes    No

**For diagnosis of non-metastatic castration-resistant or castration-sensitive prostate cancer:**

12. Does patient have any of the following risk factors? Check all that apply:
- Node positive
  - Gleason Score  $\geq 8$
  - Tumor stage T3 or T4
  - Prostate-specific antigen (PSA) concentration  $\geq 40$  ng/mL
  - Experienced prostate-specific antigen (PSA) doubling time of  $<6$  months or PSA  $\geq 20$  ng/mL on androgen deprivation therapy (e.g. GnRH analogs)

**Chart notes, labs and all diagnostic tests confirming diagnosis are required with this request**

Prescriber signature

Prescriber specialty

Date