

Reimbursement and Access Guide

Information to Support the Reimbursement and Access Process for ERLEADA[®] (apalutamide)

CONTENTS

- » Introduction
- » Indications,* Dosing, and Administration
- » Accessing ERLEADA[®]
- » Example of the Specialty Pharmacy Provider Process
- » Coding
- » Coverage Decisions
- » Resources to Support Your Janssen Patients
- » Important Safety Information

INDICATION

ERLEADA[®] (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

- Warnings and Precautions include ischemic cardiovascular events, fractures, falls, seizure, and embryo-fetal toxicity
- The most common adverse reactions ($\geq 10\%$) that occurred more frequently in the ERLEADA[®]-treated patients ($\geq 2\%$ over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture

*September 2019.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.

Introduction

This Reimbursement and Access Guide has been created to provide you and your office staff with information to assist with access for ERLEADA® (apalutamide). This guide provides information about how to access ERLEADA®, coding, guidance related to payer-approval processes, and important product information to support your patients.

- This document is presented for informational purposes only and is not intended to provide reimbursement or legal advice
- Laws, regulations, and policies concerning reimbursement are complex and updated frequently
 - While we have made an effort to be current as of the issue date of this document, the information may not be as current or comprehensive when you view it
 - Similarly, all codes are supplied for informational purposes only, and this information does not represent any statement, promise, or guarantee by Janssen Biotech, Inc., about coverage, levels of reimbursement, payment, or charge
- Please consult with your payer organization(s) for local or actual coverage and reimbursement policies and with your internal reimbursement specialist for any reimbursement or billing questions



Janssen CarePath is your one source for access, affordability, and treatment support for your patients.



Access support to help navigate payer processes

Janssen CarePath helps verify insurance coverage for your patients taking ERLEADA® and provides reimbursement information.

Online benefits investigation and prior authorization support at www.JanssenCarePathPortal.com.

[LEARN MORE](#)



Affordability support to help your patients start and stay on the treatment you prescribe

Janssen CarePath can help you find out what affordability assistance may be available for your patients taking ERLEADA®.

Comprehensive Provider Portal at www.JanssenCarePathPortal.com.

Express Enrollment Site for Savings Program at www.JanssenCarePathPortal.com/express.

[LEARN MORE](#)



Treatment support to help your patients get informed and stay on ERLEADA®

Janssen CarePath provides additional support to your patients, including patient education, web-based resources, and personalized reminders.

[LEARN MORE](#)

Call a Janssen CarePath Care Coordinator at 877-CarePath (877-227-3728), Monday - Friday, 8:00 AM to 8:00 PM ET.

Multilingual phone support available.

Sign Up or Log In to the Provider Portal at JanssenCarePathPortal.com.

Visit JanssenCarePath.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



ERLEADA® (apalutamide) Indications, Dosing, and Administration

ERLEADA® is indicated for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) or for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC).



Tablets shown are actual size.

The recommended dose of ERLEADA® is 240 mg (four 60 mg tablets) administered

ORALLY ONCE DAILY¹

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.¹



No need for co-administration of a corticosteroid.¹



Can be taken with or without food. Tablets should be swallowed whole.¹



No initial dose adjustments for ERLEADA® are necessary for renal or hepatic impairment.*¹

*ERLEADA® has not been evaluated in patients with severe renal or hepatic impairment.

Dose modifications

- If a patient experiences a \geq Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to \leq Grade 1 or original grade, and then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted¹

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.

Accessing ERLEADA[®] (apalutamide)



Specialty Distributors

- If you are an in-office dispensing pharmacy or hospital, you can order ERLEADA[®] from authorized Specialty Distributors. Please see a list of authorized Specialty Distributors below.
- All other providers and practices can contact a Specialty Pharmacy Provider (SPP). See a list of authorized SPPs on page 5.

Specialty Distributor (SD)*	Phone	Fax
ASD Healthcare	1-800-746-6273	1-800-547-9413
Besse Medical	1-800-543-2111	1-800-543-8695
Cardinal Health SD	1-877-453-3972	1-877-274-9897
Cardinal PR 120	1-800-981-4699	1-787-625-4398
McKesson Specialty Health	1-855-477-9800	N/A
McKesson Plasma and Biologics	1-877-625-2566	1-888-752-7626
Oncology Supply	1-800-633-7555	1-800-248-8205
Priority Healthcare (Curascript)	1-877-599-7748	1-800-862-6208

*This list is provided for informational purposes only. Janssen Biotech, Inc., does not endorse the use of any particular distributor. This information was current at time of publication.

Contact your specialty distributor to confirm product availability.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Seizure — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA[®] and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA[®] in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA[®]. Advise patients of the risk of developing a seizure while receiving ERLEADA[®] and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Accessing ERLEADA® (apalutamide) (cont'd)



Specialty Pharmacy Providers (SPPs)

- If you are a healthcare provider (HCP) or HCP office prescribing ERLEADA®, you can contact an SPP within the ERLEADA® distribution network
- SPPs may offer services to verify insurance coverage, identify potential patient assistance programs, and provide medication adherence support
 - For an example of the SPP process, see page 6
- Janssen CarePath can assist with identifying specialty pharmacy options that fit each patient's insurance plan

Independently Owned Specialty Pharmacies*	Phone	Fax
AcariaHealth	1-800-511-5144	1-877-541-1503
AllianceRx (Walgreens/Prime)	1-855-244-2555	1-877-231-8302
Amber Pharmacy	1-888-370-1724	1-877-645-7514
BioMatrix Specialty Pharmacy	1-888-662-6779	1-877-800-4790
BioPlus	1-888-292-0744	1-800-269-5493
Diplomat	1-877-977-9118	1-863-413-5723
Hy-Vee Pharmacy Solutions	1-877-794-9833	1-402-861-4941
Kroger Specialty Pharmacy	1-855-802-3230	1-888-315-3270
Onco360	1-877-662-6633	1-877-662-6355
Publix	1-844-797-8254	1-863-413-5723
Special Care (Puerto Rico)	1-877-899-8997	1-855-230-9963

Payer or Wholesaler-Owned Specialty Pharmacies*	Phone	Fax
Accredo	1-844-516-3319	1-888-302-1028
Aetna Specialty Pharmacy	1-866-782-2779	1-866-329-2779
Avella	1-877-546-5779	1-877-546-5780
Biologics	1-800-850-4306	1-800-823-4506
BriovaRx	1-855-427-4682	1-800-218-3221
Cigna Specialty Pharmacy Services	1-800-351-3606	1-800-351-3616
CVS Specialty Customer Care	1-800-237-2767	1-800-323-2445
Humana Specialty Pharmacy	1-800-486-2668	1-877-405-7940
US Bioservices	1-877-757-0667	1-888-899-0067

*This represents a partial list of SPPs supplying ERLEADA®. It is not intended to serve as a comprehensive list. Janssen Biotech, Inc., does not endorse the use of any of the listed pharmacies in particular.

IMPORTANT SAFETY INFORMATION

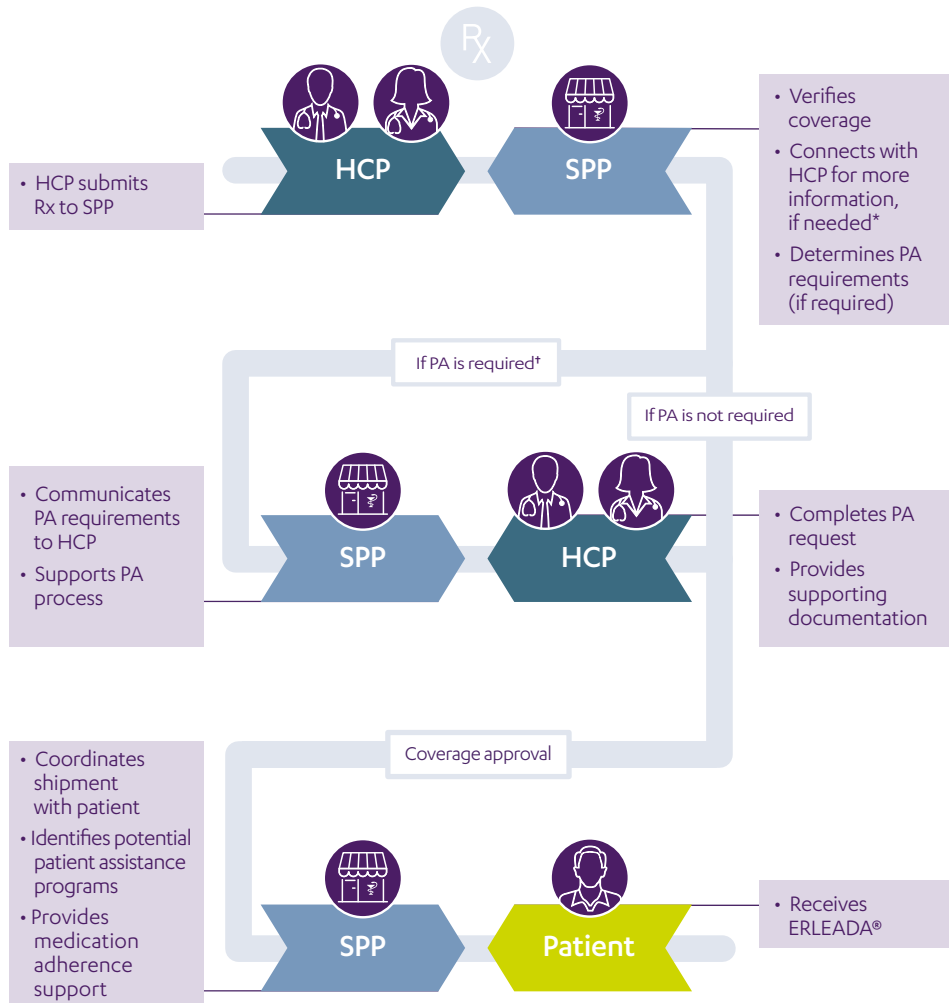
WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® [see *Use in Specific Populations* (8.1, 8.3)].

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Example of the Specialty Pharmacy Provider (SPP) Process



Janssen CarePath can help verify insurance coverage for patients, provide reimbursement information, and triage prescriptions to specialty pharmacy providers.

PA = prior authorization.

*In some cases, if a patient's insurance requires that the specialty medication be fulfilled through a specific pharmacy benefit manager-owned pharmacy, the SPP that originally received the prescription will coordinate with your staff and the approved SPP to triage the prescription.

*Also supports exception request process when applicable. If a PA submission or exception request is denied, an appeal can be filed to request that the payer reconsider the initial decision. Either the provider or the patient can initiate an appeal.

For more information on the steps outlined above, please see the [Coverage Decisions](#) section of this guide.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions ($\geq 10\%$) that occurred more frequently in the ERLEADA®-treated patients ($\geq 2\%$ over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Coding

ICD-10-CM

ICD-10-CM codes are used to identify a patient's diagnosis. The diagnosis of non-metastatic CRPC and mCSPC can be reported using a combination of the following codes:

ICD-10 code ²	Diagnosis
C61	Malignant neoplasm of prostate
R97.21	Rising PSA following treatment for malignant neoplasm of prostate
Z19.2	Hormone resistant malignancy status

ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification.

These codes are not intended to be promotional, or to encourage or suggest a use of drug that is inconsistent with FDA-approved use. Please refer to the current policy for the latest codes, since these codes are subject to change. The codes provided are not intended to be exhaustive and may require a higher level of specificity. Please consult your ICD-10 code book for additional information.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Laboratory Abnormalities — All Grades (Grade 3-4)

- Hematology** — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Coverage Decisions

Third-party payers, including both public (eg, Medicare and Medicaid) and commercial (eg, private, employer-sponsored) plans, may require more information than a prescription alone to cover a medication. There are 3 primary categories of requests for additional information:

- Prior authorization
- Exception request
- Appeals

Although there is no standardized process that applies across all payers, the goal is the same: to ensure that a prescribed medication is medically necessary and being used correctly.

Prior Authorization (PA)

Prior authorization (also called pre-authorization or pre-auth) is a common payer-required approval process that requires providers to submit medical necessity documentation in a specific way before coverage is approved for a requested therapy or service.

PA requirements – and the list of drugs subject to PA – will vary among payers. It is not unusual for there to be different coverage rules for the same therapy among payers within the same geographic area.

Often, a payer will provide a specific form or process for PA. Providers may want to supplement this with documentation providing enough detail to support the request, such as medical chart notes, laboratory results, and prescription records.

Tips for Filing a PA

Forms and documents you may want to accompany a PA submission include:

- Letter of medical necessity
- Patient Authorization form
- Copy of the patient's health plan or prescription card (front and back)
- Supporting documentation:
 - Summary of patient diagnosis
 - Date of diagnosis
 - Laboratory results and date
 - Current condition
 - Patient history and physical findings
 - Previous therapies/procedures and response to those interventions
 - Description of patient's recent symptoms/condition

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Laboratory Abnormalities — All Grades (Grade 3-4)

- **Chemistry** — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.

Coverage Decisions (cont'd)

Exception Request



Exception requests may be required when a product has been recently approved and a plan has not yet reviewed the product or made a coverage decision on it. In these cases, an exception, or nonformulary request, can be made.

An exception request is a specific type of coverage determination that asks a payer to reconsider a tiering or formulary decision. There are 2 categories of exception requests:

- **Formulary exception:** used to obtain a prescription drug that is not included on a plan's formulary or to change step therapy or quantity/dosage limits
- **Tiering exception:** used to obtain a nonpreferred drug at the cost-sharing terms applicable to drugs in the preferred tier

Enrollees, their appointed representative, or the healthcare provider may request a formulary or tiering exception. A statement from the healthcare provider supporting medical necessity will be necessary. This evidence may be submitted verbally or in writing, depending on the payer's requirements. Medicare publishes requirements for Part D plans; however, most plans will seek similar information. Exception requests are granted when a plan determines that a requested drug is medically necessary for that patient.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Rash — In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.

Coverage Decisions (cont'd)

Appeals

An appeal refers to any of the procedures used to challenge a payer's adverse coverage determination regarding benefits that a beneficiary believes he or she is entitled to receive. If a payer does not grant an exception request, that decision may be appealed.

If a PA submission or exception request is denied, an appeal can be filed to request that the payer reconsider the initial decision. Either the provider or the patient can initiate an appeal.

- Most plans allow multiple levels of appeal, which typically start with a written explanation of why the patient is clinically appropriate for the prescribed medication
- Some plans offer verbal or peer-to-peer review requests between the treating physician and the medical director at the health plan
- A non-Medicare payer may have an appeals process that is unique to that payer

Tips for Filing an Appeal



- Review the denial notice to understand the reason for denial and to identify the appeal process requirements (documentation, time frame, etc)
- Review accuracy and completeness of the original PA request (patient information, documentation, etc)
- Create a comprehensive letter of appeal (demographic, diagnostic, and treatment information)
- Include any supporting documentation as required by the payer (the denial letter, letter of medical necessity, patient records/Electronic Medical Records, etc)

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see *Dosage and Administration (2.2)*].

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Resources to Support Your Patients

Resources are available through Janssen CarePath to help assist patients to access ERLEADA® (apalutamide). Please consult with your Janssen representative for more information on the tools and resources available for your patients.

Sample Letters

Some payers and other formulary decision makers may require that treating physicians complete a Letter of Medical Necessity or request a formulary exception before patients can receive a specific therapy. We have provided a sample Letter of Medical Necessity and a sample Letter of Formulary Exception Request below.* Editable sample letter templates are available for download on JanssenCarePath.com.

Sample Letter of Medical Necessity

[Insert Physician Letterhead] cp-48234v2_4668BW018_ERLEADA_Sample LMN

[Insert Name of Medical Director] RE: Member Name: [Insert Member Name]
[Insert Payer Name] Member Number: [Insert Member Number]
[Insert Address] Group Number: [Insert Group Number]
[Insert City, State Zip]

REQUEST: Authorization for treatment with ERLEADA™ (apalutamide)
DIAGNOSIS: [Insert Diagnosis] [Insert ICD]
DOSE AND FREQUENCY: [Insert Dose & Frequency]
REQUEST TYPE: Standard EXPEDITED

Dear [Insert Name of Medical Director]:

I am writing to support my request for an **authorization** for the above-mentioned patient to receive treatment with ERLEADA™, [insert indication]. My request is supported by the following:

Summary of Patient's Diagnosis
[Insert patient's diagnosis, date of diagnosis, lab results and date, current condition]

Summary of Patient History
[Insert previous therapies/procedures, response to those interventions, description of patient's recent symptoms/condition, summary of your professional opinion of the patient's likely prognosis or disease progression without treatment with ERLEADA™. Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical condition.]

Rationale for Treatment
Considering the patient's history, condition, and the full Prescribing Information supporting uses of ERLEADA™, I believe treatment with ERLEADA™ at this time is warranted, appropriate, and medically necessary, and should be a covered and reimbursed service. Please see the accompanying [peer reviewed journal, supporting clinical guidelines, FDA approval letter and] full Prescribing Information for ERLEADA™ that provide additional clinical information to support my recommendation for ERLEADA™ for this patient.

Given the urgent nature of this request, please provide a timely authorization. Contact my office at [Insert Phone Number] if I can provide you with any additional information.

Sincerely,
[Insert Physician Name and Participating Provider Number]

If this request is denied, I am requesting an expedited Exception review by a professional in my specialty.
Enclosures [Include full Prescribing Information and the additional support noted above]

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Sample Letter of Formulary Exception Request

[Insert Physician Letterhead] cp-48535_4664W001A_ERLEADA_Sample Format Letter of Exception

Sample Format Letter of Exception

[Insert Name of Medical Director] RE: Member Name: [Insert Member Name]
[Insert Payer Name] Member Number: [Insert Member Number]
[Insert Address] Group Number: [Insert Group Number]
[Insert City, State Zip]

REQUEST: Authorization for treatment with ERLEADA™ (apalutamide)
DIAGNOSIS: [Insert Diagnosis] [Insert ICD]
DOSE AND FREQUENCY: [Insert Dose & Frequency]
REQUEST TYPE: Standard EXPEDITED

Dear [Insert Name of Medical Director]:

I am writing to request a **formulary exception** for the above-mentioned patient to receive treatment with ERLEADA™ [insert indication]. My request is supported by the following:

Summary of Patient's Diagnosis
[Insert patient's diagnosis, date of diagnosis, lab results and date, current condition]

Summary of Patient History
[Insert previous therapies/procedures, response to those interventions, description of patient's recent symptoms/condition. Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical condition.]

Rationale for Treatment
Considering the patient's history, condition, and the full Prescribing Information supporting uses of ERLEADA™, I believe treatment with ERLEADA™ at this time is warranted, appropriate, and medically necessary, and should be a covered and reimbursed service. The accompanying full Prescribing Information provides the approved clinical information for ERLEADA™.

Given the urgent nature of this request, please provide a timely authorization. Contact my office at [Insert Phone Number] if I can provide you with any additional information.

Sincerely,
[Insert Physician Name and Participating Provider Number]

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*PLEASE NOTE: These are sample letters. Use of these letters does not guarantee reimbursement.

**For questions, contact Janssen CarePath at 877-CarePath (877-227-3728),
Monday - Friday, 8:00 AM – 8:00 PM ET**

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see [page 12](#) for Important Safety Information and [click here](#) for full Prescribing Information.



Important Safety Information

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® [see *Use in Specific Populations* (8.1, 8.3)].

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)

- Hematology** — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)

- Chemistry** — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Rash — In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see *Dosage and Administration* (2.2)].

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please [click here](#) for full Prescribing Information.

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. American Medical Association. ICD-10-CM 2018; The Complete Official Code Book. Chicago, IL: Optum 360 LLC; 2017.