ONCE-DAILY

Akeega™

(niraparib/abiraterone acetate)

100mg/500mg tablets • 50mg/500mg tablets

ACCESS GUIDE

INDICATION

AKEEGA™ (niraparib and abiraterone acetate film-coated tablets) with prednisone is indicated for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for AKEEGA™.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

The safety population described in the WARNINGS and PRECAUTIONS reflect exposure to AKEEGA™ in combination with prednisone in *BRCA*m patients in Cohort 1 (N=113) of MAGNITUDE.

Myelodysplastic Syndrome/Acute Myeloid Leukemia

AKEEGA™ may cause myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

MDS/AML, including cases with fatal outcome, has been observed in patients treated with niraparib, a component of AKEEGA™.

All patients treated with niraparib who developed secondary MDS/cancer-therapy-related AML had received previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

For suspected MDS/AML or prolonged hematological toxicities, refer the patient to a hematologist for further evaluation. Discontinue AKEEGA™ if MDS/AML is confirmed.

Please read full Important Safety Information on pages 15-17 and read full Prescribing Information for AKEEGA™.

Janssen Oncology

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Table of Contents

Introduction

Janssen Biotech, Inc., is pleased to provide you with information about AKEEGA™ (niraparib and abiraterone acetate) for oral use. This Access Guide presents important product information, as well as guidelines, codes, and resources we hope will be helpful to you and your practice as you care for patients who require this therapy.

- This document is presented for informational purposes only and is not intended to provide reimbursement or legal advice, nor does it promise or guarantee coverage, levels of reimbursement, payment, or charge. Similarly, all codes are supplied for informational purposes only and represent no statement, promise, or guarantee by Janssen Biotech, Inc., that these codes will be appropriate or that reimbursement will be made. It is not intended to increase or maximize reimbursement by any payer.
- Laws, regulations, and policies concerning reimbursement are complex and are 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.
- We strongly recommend that you consult the payer organization for its coverage and reimbursement policies.

INDICATION

AKEEGA™ (niraparib and abiraterone acetate film-coated tablets) with prednisone is indicated for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for AKEEGA™.

Biomarker Testing

Biomarker tests have many uses in cancer care, including prognosis and risk assessment, screening, diagnosis, and selection of optimal treatment plans involving molecularly targeted therapies.[2] A biomarker test may be called a companion diagnostic test if it is paired with a specific treatment. Companion diagnostic laboratory tests, such as Next Generation Sequencing (NGS), report results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product.[3] Biomarker testing is a covered benefit under Medicare[3] and is typically covered by non-Medicare payers,[4] but requirements and patient cost-sharing may vary by payer:

Payer Type	Prior Authorization Requirement	Lab: In-network Requirement	Patient Cost Sharing	Verification of Benefits Recommended
Medicare ("Original")	No	Must participate in Medicare	No*	Yes
Medicare Advantage	Often	Yes	Yes†	Yes
Commercial	Often	Usually	Yes‡	Yes
Medicaid	Unknown	Must participate in Medicaid	Yes§	Yes

*No cost sharing after the annual Part B deductible is met.
†May vary by plan.
‡Varies by payer and plan.
§Often nominal; varies by state program and patient income level.

Information on FDA-approved tests for detection of *BRCA* gene alterations in mCRPC is available at:
http://www.fda.gov/CompanionDiagnostics

Coding

Results of tests that assess for deleterious variants in homologous recombination repair (HRR) genes such as *BRCA1* and *BRCA2* can be used for patients being considered for treatment with PARP inhibitors. Although often included as part of a larger panel, limited testing for a select group of genes may be done to ensure compliance with FDA-indicated drug usage where additional gene testing is not necessary, or patient does not meet criteria for larger panels.[5] When verifying benefits, you may be asked to identify the code for the requested test. The following are select codes and descriptors provided for your consideration. The codes provided are not exhaustive; additional codes may apply:

CPT® Code[6]	Descriptor[6]	Proprietary Name	Clinical Lab and/or Manufacturer
81162	*BRCA1 (BRCA1, DNA repair associated) BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)	N/A	N/A
81479	Unlisted molecular pathology procedure	N/A	N/A
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden	FoundationOne CDx™ (F1CDx)	Foundation Medicine

To order testing:

- Contact your reference laboratory to determine if the relevant test is available
- Verify the applicable CPT code
- When verifying benefits, report the specific CPT code to determine coverage and patient cost sharing

Dosage and Administration

The recommended dose of AKEEGA™ is
200 mg niraparib/1,000 mg abiraterone acetate
(two 100 mg/500 mg tablets)[1]

ORALLY ONCE DAILY[1]

- AKEEGA™ is indicated in combination with 10 mg prednisone daily[1]
- Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or have had bilateral orchiectomy.[1]

Important Administration Instructions for AKEEGA™[1]

Must be taken on an empty stomach.

Tablets must be taken as a single dose, swallowed whole with water.

Do not eat food two hours before and one hour after taking AKEEGA™.

Do not break, crush, or chew tablets.

If a dose of either AKEEGA™ or prednisone is missed, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets must not be taken to make up for the missed dose.

AKEEGA™ (niraparib and abiraterone acetate) is available in 100 mg/500 mg tablets:

Strength[1]	Package[1]	NDC[1]
100 mg/500 mg	Bottle of 60 tablets	57894-100-60

A lower-strength tablet is available if needed for dose reduction[1]:

Strength[1]	Package[1]	NDC[1]
50 mg/500 mg	Bottle of 60 tablets	57894-050-60

Dose Modification Guidelines

Under certain circumstances it may be necessary to modify the dose of AKEEGA™. The recommended dosage modifications for AKEEGA™ are provided in Table 1.

Treatment with AKEEGA™ should not be reinitiated until the toxicity has resolved to Grade 1 or baseline.[1] If the toxicity is attributed to one component of AKEEGA™, the other component of AKEEGA™ may be continued as a single agent at the current dose until the adverse reaction resolves and AKEEGA™ can be resumed.[1]

For additional information, please refer to the full AKEEGA™ **Prescribing Information**.

Table 1: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Myelosuppression *[see Warnings and Precautions (5.2)]*	Hemoglobin <8 g/dL	• Withhold AKEEGA™ and monitor blood counts weekly. • When hemoglobin returns to ≥9 g/dL, resume at the reduced dose of AKEEGA™ 100 mg/1,000 mg once daily and monitor blood counts weekly for 28 days and as clinically indicated. • Permanently discontinue AKEEGA™ if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg/1,000 mg once daily.[a]
	Platelet count <100,000/mcL	First occurrence: • Withhold AKEEGA™ for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/mcL. • Resume AKEEGA™ at same or the reduced dose of 100 mg/1,000 mg once daily. • If platelet count is <75,000/mcL, resume at the reduced dose of AKEEGA™ 100 mg/1,000 mg once daily. Second occurrence: • Withhold AKEEGA™ for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/mcL. • Resume at the reduced dose of AKEEGA™ 100 mg/1,000 mg once daily. • Permanently discontinue AKEEGA™ if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg/1,000 mg once daily.[a]

	Neutrophil <1,000/mcL	• Withhold AKEEGA™ and monitor blood counts weekly. • When neutrophil counts return to ≥1,500/mcL, resume at the reduced dose of AKEEGA™ 100 mg/1,000 mg once daily and monitor blood counts weekly for 28 days and as clinically indicated. • Permanently discontinue AKEEGA™ if neutrophils have not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg/1,000 mg once daily.[a]
	Hematologic adverse reaction requiring transfusion	• Consider platelet transfusion for patients with platelet count ≤10,000/mcL. If there are other risk factors such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Resume at the reduced dose of AKEEGA™ 100 mg/1,000 mg once daily.
Hepatotoxicity *[see Warnings and Precautions (5.4)]*	ALT and/or AST greater than 5 × ULN or total bilirubin greater than 3 × ULN	• Withhold AKEEGA™ and closely monitor liver function. • Permanently discontinue AKEEGA™ if: ALT or AST ≥20 times the ULN – OR– ALT >3 × ULN and total bilirubin >2 × ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation -OR- Hepatotoxicity recurs at the reduced dose of 100 mg/500 mg. • When AST and ALT resolves to ≤2.5 × ULN and total bilirubin ≤1.5 × ULN, AKEEGA™ may be resumed at the reduced dose of 100 mg/500 mg once daily. When resumed, monitor serum transaminases every two weeks for three months, monthly thereafter, and as clinically indicated.
Other non-hematological adverse reactions that persist despite medical management *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*	Grade 3 or 4[b]	• Withhold AKEEGA™ until resolution of adverse reaction or for a maximum of 28 days. • If resolves in 28 days or less, AKEEGA™ may be resumed at the reduced dose. • Permanently discontinue AKEEGA™ if adverse reaction(s) has not resolved after 28 days or Grade 3 or 4 adverse reaction reoccurs after dose reduction.

[a]If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue AKEEGA™ *[see Warnings and Precautions (5.1)]*.
[b]Discontinue AKEEGA™ in patients who develop hypertensive crisis or other severe cardiovascular adverse reactions *[see Warnings and Precautions (5.3)]*.

Patient Monitoring

Complete Blood Counts[1]

AKEEGA™ may cause myelosuppression (anemia, thrombocytopenia, or neutropenia).

Monitor complete blood counts weekly during the first month of AKEEGA™ treatment, every two weeks for the next two months, monthly for the remainder of the first year and then every other month, and as clinically indicated.

Liver Function Tests[1]

AKEEGA™ may cause hepatotoxicity. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with AKEEGA™, every two weeks for the first three months of treatment and monthly thereafter.

Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions[1]

AKEEGA™ may cause hypokalemia and fluid retention. In post-marketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking abiraterone acetate, a component of AKEEGA™. Hypertension and hypertensive crisis have also been reported in patients treated with niraparib, a component of AKEEGA™.[1]

Monitor patients for hypertension, hypokalemia, and fluid retention at least weekly for the first two months, then once a month. Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before and during treatment with AKEEGA™.[1]

Table 2: Patient Monitoring Summary

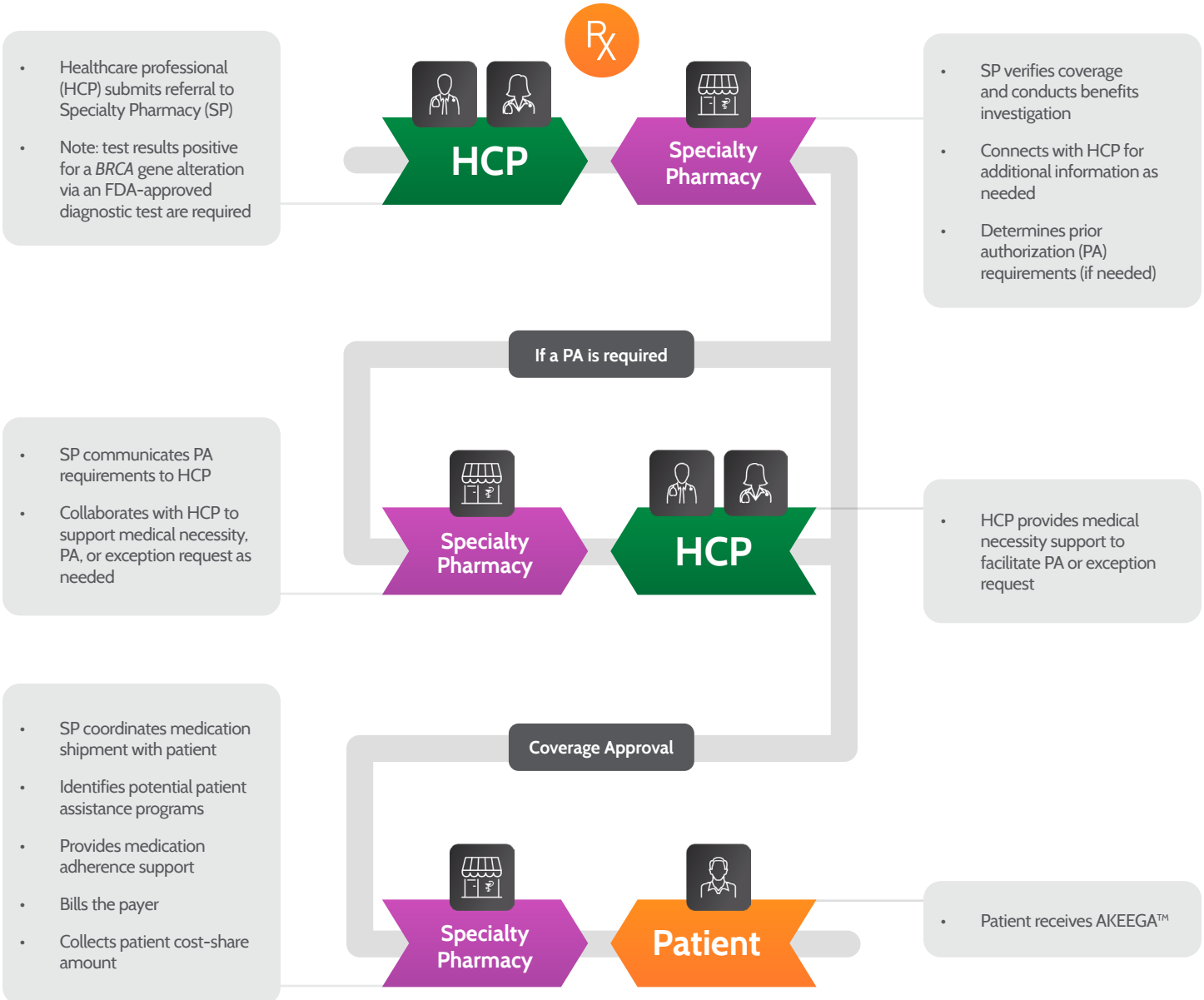
MONITORING COMPONENT	THERAPY DURATION					
	Pre-treatment	Month #1	Month #2	Month #3	Months #4 - #12	Ongoing
Complete Blood Count	✓	weekly	every 2 weeks	every 2 weeks	monthly	every other month and as clinically indicated
Liver Function Tests	✓	every 2 weeks	every 2 weeks	every 2 weeks	monthly	monthly
Serum Potassium	✓	weekly	weekly	monthly	monthly	monthly
Fluid Retention	✓	weekly	weekly	monthly	monthly	monthly
Blood Pressure	✓	weekly	weekly	monthly	monthly	monthly

Accessing AKEEGA™

AKEEGA™ is available through the following Specialty Pharmacy:

Specialty Pharmacy	Phone	Fax	Website	ePrescribe
Onco360	(877) 662-6633	(877) 662-6355	https://onco360.com/	Oncomed DBA Onco360 or NPI# 1679618151

Example of the Specialty Pharmacy Process



- Healthcare professional (HCP) submits referral to Specialty Pharmacy (SP)
- Note: test results positive for a *BRCA* gene alteration via an FDA-approved diagnostic test are required

- SP verifies coverage and conducts benefits investigation
- Connects with HCP for additional information as needed
- Determines prior authorization (PA) requirements (if needed)

- SP communicates PA requirements to HCP
- Collaborates with HCP to support medical necessity, PA, or exception request as needed

- HCP provides medical necessity support to facilitate PA or exception request

- SP coordinates medication shipment with patient
- Identifies potential patient assistance programs
- Provides medication adherence support
- Bills the payer
- Collects patient cost-share amount

- Patient receives AKEEGA™

Supporting Payer Coverage Decisions

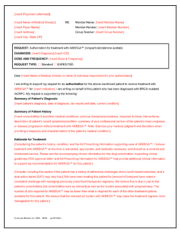
Third-party payers, both public (eg, Medicare and Medicaid) and commercial (eg, private, employer-sponsored), may require more than a prescription to cover AKEEGA™. A summary of the medical necessity of treatment and specific responses to prior authorization (PA) requirements are often necessary. If the payer determines the initial information inadequate to grant coverage, it may also be necessary to request an exception or support an appeal.

Medical Necessity

Medical necessity refers to healthcare services or supplies needed to diagnose or treat an illness, injury, condition, disease, or its symptoms, and that meet accepted standards of medicine. Generally, payers provide coverage only for health-related services they determine to be medically necessary. Payer policies define medical necessity criteria, including indications (ie, diagnosis codes), required diagnostic test results (eg, lab results, x-ray findings, etc.), and any limitations of coverage that may apply. When third-party payers consider coverage requests for AKEEGA™, they will first determine if the therapy is covered under their policies. Next, they will look for evidence supporting medical necessity, which may include, but not be limited to:

- Patient diagnosis and alignment with indications for requested therapy
- Biomarker test results (positive for a *BRCA* gene alteration)
- Summary of patient's current medical condition and history, including previous therapies and outcomes
- Rationale for requested therapy and expected outcome(s)

Some payers may require the prescribing physician to submit a Letter of Medical Necessity (LMN) summarizing these points.



Click here to download the Sample Letter of Medical Necessity and Exception Letter for AKEEGA™.

Diagnosis Coding

ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) is a system used by physicians and other healthcare providers to classify and code diagnoses and symptoms. Diagnosis codes support the rationale for a requested treatment. When prescribing AKEEGA™ it is necessary to provide the patient's diagnosis to the dispensing specialty pharmacy. The diagnosis of metastatic castration-resistant prostate cancer (mCRPC) can be reported using a combination of the following codes:

ICD-10-CM Code[7]	Description[7]
C61	Malignant neoplasm of prostate
Z19.2	Hormone resistant malignancy status
R97.21	Rising PSA following treatment for malignant neoplasm of prostate
Z15.03	Genetic susceptibility to malignant neoplasm of prostate
C77.xx-C80.0; C7B	Metastatic disease

These codes are not intended to be promotional or to encourage or suggest a use of drug that is inconsistent with FDA-approved use. The codes provided are not exhaustive and additional codes may apply.

Supporting Payer Coverage Decisions (cont'd)

Prior Authorization

Prior authorization (PA) is a common payer process that requires establishing medical necessity while also meeting specific payer coverage criteria. Many therapies are subject to PA, but the process and list of drugs 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 applicable, nationally recognized, clinical practice guidelines.

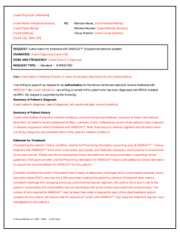
Tips for Filing a PA

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 (positive for *BRCA* gene alteration)
    - Current condition
  - Patient history and physical findings
    - Previous therapies/procedures and response to those interventions
    - Description of patient's recent symptoms/condition

Exception Requests

An exception is a type of coverage determination that may apply when a product has been recently approved and a plan has not yet made a coverage decision (eg, is not on formulary or subject to a "new-to-market" block) or if a payer's coverage requirements cannot be met. A request for exception asks that the restrictions placed on a specific medication be released as the therapy is medically appropriate and necessary for a patient's treatment. It provides a payer the opportunity to move to an individualized, patient-centered decision-making process when the payer's coverage policies do not meet a patient's unique needs. It is generally necessary for prescribers to submit a supporting statement providing details about the rationale for the request. Payer policies and processes, including the time in which a decision is to be expected, can vary.



Click here to download the Sample Letter of Medical Necessity and Exception Letter for AKEEGA™.

Supporting Payer Coverage Decisions (cont'd)

Appeals

An appeal is any of the procedures used to challenge a payer's denial of benefits that a beneficiary believes they are entitled to receive. If a payer denies an initial request for coverage, or an exception request, the decision may be appealed. The payer's notice of denial should include the reason for that decision, as well as instructions for filing an appeal. Most plans have multiple, progressive levels of appeal, allowing beneficiaries to continue advancing their request if initial efforts are not successful.

Appeals may be initiated by the patient or their healthcare provider. No matter the origin, it is generally necessary for prescribers to submit a supporting statement providing details 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.

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, etc.)

Support and Resources

To help you get your patients started on AKEEGA™, the following resources may be helpful to your patients and your practice:

- Janssen CarePath Oncology Resource Guide
  Janssen CarePath is your one source for access, affordability, and treatment support for your patients. Our dedicated Care Coordinator team supports the Janssen medications you prescribe. We can help make it easier for you and your patients to get the resources you both may need.
- Janssen CarePath Pharmacy Benefit Investigation Form (BIF)
  This form allows for both benefit investigation as well as sign up for all patient support for AKEEGA™, including the AKEEGA™ Co-pay Support Program and the *Janssen Compass*® Care Navigator Support.
- Supporting Appropriate Payer Coverage Decisions

  This brochure has been developed to help healthcare providers understand how to work with payers for coverage of medically necessary drug therapies.
- Extra Help With Prescription Drug Costs: Medicare Low-Income Subsidy (LIS) Overview

  Learn about extra help available to low-income residents of the United States who are enrolled in Medicare Prescription Drug Plans.
- Know Your State Interactive Tool

  This interactive tool provides information on affordability options for patients at the state level.
- Prior Authorization Considerations Checklist

  Learn more about general prior authorization processes, including items and information that may be requested from your patient's insurer.
- Appeal Considerations Checklist

  If your patient's insurer denies coverage for your patient, learn more about general insurance appeal processes.
- Exception Considerations Checklist

  General information on exception processes for your patient's coverage of medically necessary drug therapies.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

The safety population described in the WARNINGS and PRECAUTIONS reflect exposure to AKEEGA™ in combination with prednisone in *BRCA*m patients in Cohort 1 (N=113) of MAGNITUDE.

Myelodysplastic Syndrome/Acute Myeloid Leukemia

AKEEGA™ may cause myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

MDS/AML, including cases with fatal outcome, has been observed in patients treated with niraparib, a component of AKEEGA™.

All patients treated with niraparib who developed secondary MDS/cancer-therapy-related AML had received previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

For suspected MDS/AML or prolonged hematological toxicities, refer the patient to a hematologist for further evaluation. Discontinue AKEEGA™ if MDS/AML is confirmed.

Myelosuppression

AKEEGA™ may cause myelosuppression (anemia, thrombocytopenia, or neutropenia).

In MAGNITUDE Cohort 1, Grade 3-4 anemia, thrombocytopenia, and neutropenia were reported, respectively in 28%, 8%, and 7% of patients receiving AKEEGA™. Overall, 27% of patients required a red blood cell transfusion, including 11% who required multiple transfusions. Discontinuation due to anemia occurred in 3% of patients.

Monitor complete blood counts weekly during the first month of AKEEGA™ treatment, every two weeks for the next two months, monthly for the remainder of the first year and then every other month, and as clinically indicated. Do not start AKEEGA™ until patients have adequately recovered from hematologic toxicity caused by previous therapy. If hematologic toxicities do not resolve within 28 days following interruption, discontinue AKEEGA™ and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics.

Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions

AKEEGA™ may cause hypokalemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. In post-marketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking abiraterone acetate, a component of AKEEGA™. Hypertension and hypertensive crisis have also been reported in patients treated with niraparib, a component of AKEEGA™.

In MAGNITUDE Cohort 1, which used prednisone 10 mg daily in combination with AKEEGA™, Grades 3-4 hypokalemia was detected in 2.7% of patients on the AKEEGA™ arm and Grades 3-4 hypertension were observed in 14% of patients on the AKEEGA™ arm.

The safety of AKEEGA™ in patients with New York Heart Association (NYHA) Class II to IV heart failure has not been established because these patients were excluded from MAGNITUDE.

Monitor patients for hypertension, hypokalemia, and fluid retention at least weekly for the first two months, then once a month. Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before and during treatment with AKEEGA™.

Discontinue AKEEGA™ in patients who develop hypertensive crisis or other severe cardiovascular adverse reactions.

Hepatotoxicity

AKEEGA™ may cause hepatotoxicity.

Hepatotoxicity in patients receiving abiraterone acetate, a component of AKEEGA™, has been reported in clinical trials. In post-marketing experience, there have been abiraterone acetate-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure, and deaths.

In MAGNITUDE Cohort 1, Grade 3-4 ALT or AST increases (at least 5 x ULN) were reported in 1.8% of patients. The safety of AKEEGA™ in patients with moderate or severe hepatic impairment has not been established as these patients were excluded from MAGNITUDE.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity (continued)

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with AKEEGA™, every two weeks for the first three months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring and may require dosage modifications.

Permanently discontinue AKEEGA™ for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation, or in patients who develop ALT or AST ≥20 x ULN at any time after receiving AKEEGA™.

Adrenocortical Insufficiency

AKEEGA™ may cause adrenal insufficiency.

Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate, a component of AKEEGA™, in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased doses of corticosteroids may be indicated before, during, and after stressful situations.

Hypoglycemia

AKEEGA™ may cause hypoglycemia in patients being treated with other medications for diabetes.

Severe hypoglycemia has been reported when abiraterone acetate, a component of AKEEGA™, was administered to patients receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide.

Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with AKEEGA™. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Increased Fractures and Mortality in Combination with Radium 223 Dichloride

AKEEGA™ with prednisone is not recommended for use in combination with Ra-223 dichloride outside of clinical trials.

The clinical efficacy and safety of concurrent initiation of abiraterone acetate plus prednisone/prednisolone and radium Ra 223 dichloride was assessed in a randomized, placebo-controlled multicenter study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee recommendation.

At the primary analysis, increased incidences of fractures (29% vs 11%) and deaths (39% vs 36%) have been observed in patients who received abiraterone acetate plus prednisone/prednisolone in combination with radium Ra 223 dichloride compared to patients who received placebo in combination with abiraterone acetate plus prednisone.

It is recommended that subsequent treatment with Ra-223 not be initiated for at least five days after the last administration of AKEEGA™, in combination with prednisone.

Posterior Reversible Encephalopathy Syndrome

AKEEGA™ may cause Posterior Reversible Encephalopathy Syndrome (PRES).

PRES has been observed in patients treated with niraparib as a single agent at higher than the recommended dose of niraparib included in AKEEGA™.

Monitor all patients treated with AKEEGA™ for signs and symptoms of PRES. If PRES is suspected, promptly discontinue AKEEGA™ and administer appropriate treatment. The safety of reinitiating AKEEGA™ in patients previously experiencing PRES is not known.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Embryo-Fetal Toxicity

The safety and efficacy of AKEEGA™ have not been established in females. Based on animal reproductive studies and mechanism of action, AKEEGA™ can cause fetal harm and loss of pregnancy when administered to a pregnant female.

Niraparib has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow).

In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of AKEEGA™. Females who are or may become pregnant should handle AKEEGA™ with protection, e.g., gloves.

Based on animal studies, AKEEGA™ may impair fertility in males of reproductive potential.

ADVERSE REACTIONS

The safety of AKEEGA™ in patients with *BRCA*m mCRPC was evaluated in Cohort 1 of MAGNITUDE.

The most common adverse reactions (≥10%), including laboratory abnormalities, are decreased hemoglobin, decreased lymphocytes, decreased white blood cells, musculoskeletal pain, fatigue, decreased platelets, increased alkaline phosphatase, constipation, hypertension, nausea, decreased neutrophils, increased creatinine, increased potassium, decreased potassium, increased AST, increased ALT, edema, dyspnea, decreased appetite, vomiting, dizziness, COVID-19, headache, abdominal pain, hemorrhage, urinary tract infection, cough, insomnia, increased bilirubin, weight decreased, arrhythmia, fall, and pyrexia.

Serious adverse reactions reported in >2% of patients included COVID-19 (7%), anemia (4.4%), pneumonia (3.5%), and hemorrhage (3.5%). Fatal adverse reactions occurred in 9% of patients who received AKEEGA™, including COVID-19 (5%), cardiopulmonary arrest (1%), dyspnea (1%), pneumonia (1%), and septic shock (1%).

DRUG INTERACTIONS

Effect of Other Drugs on AKEEGA™

Avoid coadministration with strong CYP3A4 inducers.

Abiraterone is a substrate of CYP3A4. Strong CYP3A4 inducers may decrease abiraterone concentrations, which may reduce the effectiveness of abiraterone.

Effects of AKEEGA™ on Other Drugs

Avoid coadministration unless otherwise recommended in the Prescribing Information for CYP2D6 substrates for which minimal changes in concentration may lead to serious toxicities. If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug.

Abiraterone is a CYP2D6 moderate inhibitor. AKEEGA™ increases the concentration of CYP2D6 substrates, which may increase the risk of adverse reactions related to these substrates.

Monitor patients for signs of toxicity related to a CYP2C8 substrate for which a minimal change in plasma concentration may lead to serious or life-threatening adverse reactions.

Abiraterone is a CYP2C8 inhibitor. AKEEGA™ increases the concentration of CYP2C8 substrates, which may increase the risk of adverse reactions related to these substrates.

Please see the full Prescribing Information for AKEEGA™.

cp-401051v1

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