

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216793Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AKEEGA safely and effectively. See full prescribing information for AKEEGA.

AKEEGA™ (niraparib and abiraterone acetate) tablets, for oral use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

AKEEGA is a combination of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, and abiraterone acetate, a CYP17 inhibitor indicated with prednisone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for AKEEGA. (1, 2.1)

DOSAGE AND ADMINISTRATION

The recommended dosage of AKEEGA is 200 mg niraparib/1,000 mg abiraterone acetate orally once daily in combination with 10 mg prednisone daily until disease progression or unacceptable toxicity. (2.2)

Patients receiving AKEEGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.2)

Take AKEEGA on an empty stomach. Do not eat food two hours before and one hour after taking AKEEGA. (2.2)

For adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 50 mg niraparib/500 mg abiraterone acetate (3)
- 100 mg niraparib/500 mg abiraterone acetate (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- 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. Monitor patients for hematological toxicity and discontinue if MDS/AML is confirmed. (5.1)
- Myelosuppression: Test complete blood counts weekly for the first month, every two weeks for the next two months, monthly for the remainder of the first year, then every other month, and as clinically indicated. (2.3, 5.2)
- Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions: 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. Control

hypertension and correct hypokalemia before and during treatment with AKEEGA. (5.3)

- Hepatotoxicity: Can be severe and fatal. Monitor liver function and modify, interrupt, or discontinue treatment as recommended. (2.3, 5.4)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.5)
- Hypoglycemia: 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 assess if antidiabetic agent dose modifications are required. (5.6)
- Increased fractures and mortality in combination with radium Ra 223 dichloride: Use of AKEEGA plus prednisone in combination with radium Ra 223 dichloride is not recommended. (5.7)
- Posterior Reversible Encephalopathy Syndrome (PRES): PRES has been observed in patients treated with niraparib, a component of AKEEGA. Discontinue AKEEGA if PRES is confirmed. (5.8)
- Embryo-Fetal Toxicity: AKEEGA can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception. (5.9, 8.1, 8.3)

ADVERSE REACTIONS

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Avoid coadministration. (7.1)
- CYP2D6 Substrates: Avoid coadministration of AKEEGA with 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. (7.2)

USE IN SPECIFIC POPULATIONS

- Moderate or Severe Hepatic impairment: Avoid use. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AKEEGA 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 [see *Dosage and Administration* (2.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of mCRPC with AKEEGA based on the presence of a *BRCA* gene alteration [see *Clinical Studies* (14)].

Information on FDA-approved tests is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended dosage of AKEEGA is 200 mg niraparib/1,000 mg abiraterone acetate orally once daily in combination with 10 mg prednisone daily until disease progression or unacceptable toxicity.

Patients receiving AKEEGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Take AKEEGA on an empty stomach. Do not eat food two hours before and one hour after taking AKEEGA. Swallow tablets whole with water. Do not break, crush, or chew tablets.

If a patient misses a dose, instruct patients to take the dose as soon as possible on the same day and resume their next dose at the normal schedule the following day.

2.3 Dosage Modification for Adverse Reactions

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. 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 (see Table 1).

Table 1: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Myelosuppression [see <i>Warnings and Precautions</i> (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 $\geq 100,000/\text{mcL}$. • 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 $\geq 100,000/\text{mcL}$. • 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 $\geq 1,500/\text{mcL}$, 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 $\leq 10,000/\text{mcL}$. 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 $5 \times \text{ULN}$ or total bilirubin greater than $3 \times \text{ULN}$	- Withhold AKEEGA and closely monitor liver function. - Permanently discontinue AKEEGA if: ALT or AST ≥ 20 times the ULN – OR – ALT $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$ in the absence of biliary obstruction or other causes responsible for the concurrent elevation -OR- Hepatotoxicity recurs at the reduced dose 100 mg/500 mg. - When AST and ALT resolves to less $\leq 2.5 \times \text{ULN}$ and total bilirubin $\leq 1.5 \times \text{ULN}$, 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.
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- ^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)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 50 mg niraparib/500 mg abiraterone acetate: yellowish orange to yellowish brown, oval, film-coated tablets debossed with “N 50 A” on one side and plain on the other side.
- 100 mg niraparib/500 mg abiraterone acetate: orange, oval, film-coated tablets debossed with “N 100 A” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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 [see *Dosage and Administration* (2.3)].

5.3 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 [see *Clinical Pharmacology* (12.1)]. 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.

5.4 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.

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 [see *Dosage and Administration* (2.3)].

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 $\geq 20 \times$ ULN at any time after receiving AKEEGA.

5.5 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.

5.6 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 [*see Drug Interactions (7.2)*].

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.

5.7 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.

5.8 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.

5.9 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 [see *Clinical Pharmacology* (12.1)].

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) [see *Warnings and Precautions* (5.2) and *Nonclinical Toxicology* (13.1)].

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 [see *Use in Specific Populations* (8.1, 8.3)]. Females who are or may become pregnant should handle AKEEGA with protection, e.g., gloves [see *How Supplied/Storage and Handling* (16)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic syndrome/acute myeloid leukemia [see *Warnings and Precautions* (5.1)]
- Myelosuppression [see *Warnings and Precautions* (5.2)]
- Hypokalemia, fluid retention, and cardiovascular adverse reactions [see *Warnings and Precautions* (5.3)]
- Hepatotoxicity [see *Warnings and Precautions* (5.4)]
- Adrenocortical insufficiency [see *Warnings and Precautions* (5.5)]
- Hypoglycemia [see *Warnings and Precautions* (5.6)]
- Increased fractures and mortality in combination with Radium 223 Dichloride [see *Warnings and Precautions* (5.7)]
- Posterior reversible encephalopathy syndrome [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the WARNINGS and PRECAUTIONS reflect exposure to AKEEGA (niraparib 200 mg and abiraterone acetate 1,000 mg) in combination with prednisone 10 mg once daily in *BRCA*-mutated patients in Cohort 1 (N=113) of MAGNITUDE.

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer

The safety of AKEEGA in patients with *BRC*Am mCRPC was evaluated in Cohort 1 of MAGNITUDE [see *Clinical Studies (14.1)*]. Patients were randomized to receive either AKEEGA (niraparib 200 mg and abiraterone acetate 1,000 mg once daily) (n=113), or placebo and abiraterone acetate (n=112) until unacceptable toxicity or progression. Patients in both arms also received prednisone 10 mg daily. The median duration of exposure for AKEEGA was 18 months (range: 0 to 37 months).

Serious adverse reactions occurred in 41% of patients who received AKEEGA. 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%).

Permanent discontinuation of any component of AKEEGA due to an adverse reaction occurred in 15% of patients. Adverse reactions which resulted in permanent discontinuation of AKEEGA in > 2% of patients included COVID-19 (4.4%), anemia (2.7%), asthenia (2.7%), and vomiting (2.7%).

Dosage interruptions of any component of AKEEGA due to an adverse reaction occurred in 50% of patients. Adverse reactions which required dosage interruption in > 2% of patients included anemia (23%), thrombocytopenia (12%), neutropenia (7%), COVID-19 (6%), fatigue (3.5%), asthenia (3.5%), nausea (3.5%), pneumonia (2.7%), hematuria (2.7%), and vomiting (2.7%).

Dose reductions of any component of AKEEGA due to an adverse reaction occurred in 28% of patients. Adverse reactions which required dose reductions in > 2% of patients included anemia (12%), thrombocytopenia (4.4%), and fatigue (2.7%).

The most common adverse reactions (>10%) in patients who received AKEEGA were musculoskeletal pain, fatigue, constipation, hypertension, nausea, edema, dyspnea, decreased appetite, vomiting, dizziness, COVID-19, headache, abdominal pain, hemorrhage, urinary tract infection, cough, insomnia, weight decreased, arrhythmia, fall, and pyrexia.

The most common select laboratory abnormalities (>10%) that worsened from baseline in patients who received AKEEGA were hemoglobin decreased, platelets decreased, neutrophils decreased, creatinine increased, potassium decreased, AST increased, ALT increased, and bilirubin increased.

Tables 2 and 3 summarize adverse reactions and laboratory abnormalities for patients with *BRCAm* mCRPC in MAGNITUDE, respectively.

Table 2: Adverse Reactions (>10%) in Patients with *BRCAm* mCRPC Who Received AKEEGA in MAGNITUDE

Adverse Reaction	AKEEGA with Prednisone N=113		Placebo with Abiraterone Acetate and Prednisone N=112	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Musculoskeletal pain ^a	44	4	42	5
Fatigue ^a	43	5	30	4
Constipation	34	1	20	0
Hypertension ^a	33	14	27	17
Nausea	33	1	21	0
Edema ^a	17	0	9	0
Dyspnea ^a	15	1	8	3
Decreased appetite	15	2	8	0
Vomiting	15	0	7	1
Dizziness ^a	14	0	10	0
COVID-19 ^a	13	7	9	4
Abdominal pain ^a	12	2	12	1
Hemorrhage ^a	12	2	8	1
Headache	12	1	9	0
Urinary tract infection ^a	12	3	9	1
Cough ^a	12	0	6	0
Insomnia	12	0	4	0
Weight decreased	10	1	4	1
Arrhythmia ^a	10	2	4	1
Fall	10	1	13	4
Pyrexia ^a	10	2	6	0

^a Includes multiple similar terms.

Clinically relevant adverse events that occurred in <10% of patients receiving niraparib and abiraterone acetate plus prednisone were rash (7%), ALT increased (5%), AST increased (5%), cerebrovascular accident (4.4%), pulmonary embolism (2.7%), deep vein thrombosis (2.7%), and acute kidney injury (2.7%).

Table 3: Select Laboratory Abnormalities (>10%) That Worsened from Baseline in Patients with *BRCAm* mCRPC Who Received AKEEGA in MAGNITUDE

Laboratory Abnormality	AKEEGA with Prednisone ¹ N=113		Placebo with Abiraterone Acetate and Prednisone ¹ N=112	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Hemoglobin decreased	67	26	53	7
Lymphocyte decreased	55	22	32	13
WBC decreased	48	6	18	0.9

Platelets decreased	37	8	22	1.8
Neutrophils decreased	32	7	16	2.7
Chemistry				
ALP increased	34	1.8	29	1.8
Creatinine increased	30	0	13	1.8
Potassium increased	25	0.9	21	3.6
Potassium decreased	20	5	20	5
AST increased	20	1.8	25	2.7
ALT increased	18	0.9	17	4.5
Bilirubin increased	12	0	10	0.9

¹ The denominator used to calculate the rate varied from 111 to 112 for placebo with abiraterone acetate and prednisone and 113 for AKEEGA with prednisone based on the number of patients with a baseline value and at least one post-treatment value.

Other Clinical Trial Experience

The following adverse reactions have been reported with the individual components of AKEEGA but were not observed in MAGNITUDE Cohort 1: myopathy, rhabdomyolysis, adrenal insufficiency, allergic alveolitis, febrile neutropenia, anaphylactic reaction, posterior reversible encephalopathy (PRES), hypertensive crisis, and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on AKEEGA

Effect of CYP3A4 Inducers

Avoid coadministration with strong CYP3A4 inducers [*see Clinical Pharmacology (12.3)*].

Abiraterone is a substrate of CYP3A4. Strong CYP3A4 inducers may decrease abiraterone concentrations [*see Clinical Pharmacology (12.3)*], which may reduce the effectiveness of abiraterone.

7.2 Effects of AKEEGA on Other Drugs

CYP2D6 Substrates

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 [*see Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions related to these substrates.

CYP2C8 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 [see *Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions related to these substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of AKEEGA have not been established in females. Based on findings from animal studies and mechanism of action [see *Clinical Pharmacology (12.1)*], AKEEGA can cause fetal harm and potential loss of pregnancy.

There are no human data on the use of AKEEGA in pregnant women.

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) [see *Warnings and Precautions (5.2)* and *Nonclinical Toxicology (13.1)*]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

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 (see *Data*).

Data

Animal Data

Niraparib

Niraparib is genotoxic and targets actively dividing cells. Animal developmental and reproductive toxicology studies were not conducted with niraparib.

Abiraterone Acetate

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥ 10 mg/kg/day, decreased fetal ano-genital distance at ≥ 30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥ 10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients receiving 1,000 mg daily of abiraterone acetate.

8.2 Lactation

Risk Summary

The safety and efficacy of AKEEGA have not been established in females. There is no information available on the presence of niraparib or abiraterone in human milk, or on the effects on the breastfed child or milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies and its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of AKEEGA [see *Use in Specific Populations* (8.1)].

Infertility

Based on animal studies, AKEEGA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

Safety and effectiveness of AKEEGA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 113 patients with *BRCA* gene alteration(s) who received AKEEGA in MAGNITUDE, 34.5% of patients were less than 65 years, 38.9% of patients were 65 years to 74 years, and 26.5% were 75 years and over.

There was an insufficient number of patients with *BRCA* gene alteration(s) treated with AKEEGA in MAGNITUDE to accurately characterize efficacy or safety by age.

8.6 Hepatic Impairment

Avoid use of AKEEGA in patients with moderate or severe hepatic impairment [see *Warnings and Precautions* (5.4) and *Clinical Pharmacology* (12.3)].

No dosage modification is necessary for patients with mild hepatic impairment.

8.7 Renal Impairment

Monitor patients with severe renal impairment for increased adverse reactions and modify dosage as recommended for adverse reactions [see *Clinical Pharmacology* (12.3)].

No dosage modification is recommended for patients with mild to moderate renal impairment.

10 OVERDOSAGE

In the event of an overdose, administration of AKEEGA should be stopped and general supportive measures undertaken, including monitoring for arrhythmias and cardiac failure and assessing liver function.

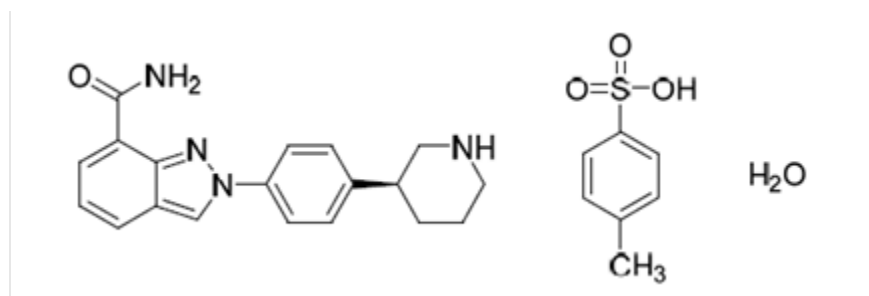
There is no specific treatment in the event of AKEEGA overdose.

11 DESCRIPTION

AKEEGATM (niraparib and abiraterone acetate) tablets contain niraparib tosylate (as the monohydrate) and abiraterone acetate.

Niraparib

Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. The chemical name for niraparib tosylate monohydrate is 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). The molecular formula is C₂₆H₃₀N₄O₅S and it has a molecular weight of 510.61 g/mol. The molecular structure is shown below:

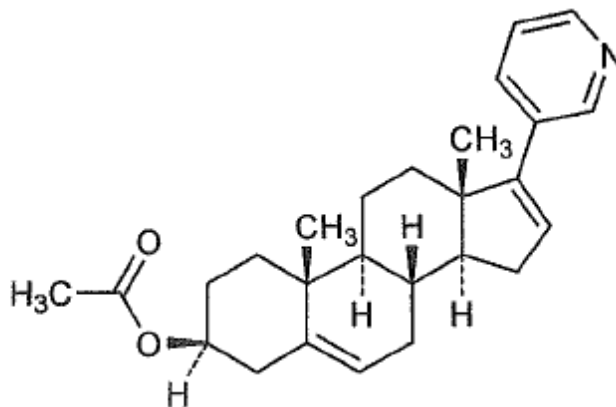


Niraparib tosylate monohydrate is a white to off-white, non-hygroscopic crystalline solid. Niraparib tosylate monohydrate is highly soluble in aqueous media over the pH range 1.2 to 6.8 (1.65-1.77 mg/mL determined at 37 ± 1°C).

Abiraterone Acetate

Abiraterone acetate is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17 α -hydroxylase/C17,20-lyase). Its molecular formula is C₂₆H₃₃NO₂ and it has a molecular

weight of 391.55 g/mol. Abiraterone acetate is designated chemically as (3 β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

AKEEGA tablets are supplied as 50 mg/500 mg niraparib/abiraterone acetate and 100 mg/500 mg niraparib/abiraterone acetate film-coated tablets for oral administration.

Each AKEEGA tablet (50 mg/500 mg) contains 50 mg of niraparib (equivalent to 76.9 mg niraparib tosylate) and 500 mg of abiraterone acetate.

Each AKEEGA tablet (100 mg/500 mg) contains 100 mg of niraparib (equivalent to 153.7 mg niraparib tosylate) and 500 mg of abiraterone acetate.

AKEEGA tablet core contains the following inactive ingredients: colloidal anhydrous silica, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, sodium lauryl sulfate.

- The 50 mg/500 mg tablets are finished with film-coating comprising the following inactive ingredients: iron oxide black, iron oxide red, iron oxide yellow, sodium lauryl sulphate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide.
- The 100 mg/500 mg tablets are finished with film-coating comprising the following inactive ingredients: iron oxide red, iron oxide yellow, sodium lauryl sulphate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Niraparib is an inhibitor of PARP enzymes, including PARP-1 and PARP-2, that play a role in DNA repair. *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased niraparib-induced cytotoxicity was observed in tumor

cell lines with or without deficiencies in *BRCA1/2*. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA1/2* and in human patient-derived xenograft tumor models with homologous recombination deficiency (HRD) that had either mutated or wild-type *BRCA1/2*.

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17 α -hydroxy derivatives by 17 α -hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals [*see Warnings and Precautions (5.9)*].

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

Abiraterone decreased serum testosterone and other androgens in patients in the placebo-controlled clinical trial. It is not necessary to monitor the effect of abiraterone on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

In mouse xenograft models of prostate cancer, the combination of niraparib and abiraterone acetate increased anti-tumor activity when compared to either drug alone.

12.2 Pharmacodynamics

The exposure-response relationship and time-course of pharmacodynamic response for the safety and effectiveness of AKEEGA have not been fully characterized.

Hypertension and Cardiovascular Effects

Niraparib has the potential to cause effects on pulse rate and blood pressure in patients, which may be related to pharmacological inhibition of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT) [*see Nonclinical Toxicology (13.2)*].

Niraparib increased mean pulse rate by 22.4 to 24.1 beats/min, mean systolic blood pressure by 24.5 mmHg, and mean diastolic pressure by 16.5 mmHg relative to 14.0 to 15.8 beats per min, 18.3 to 19.6 mmHg, and 11.6 mmHg in the placebo arm.

Cardiac Electrophysiology

No large (>20 ms) increases in the mean QTc interval were detected following the treatment of niraparib 300 mg once daily or 1,000 mg of abiraterone acetate once daily.

12.3 Pharmacokinetics

Niraparib

Following the administration of AKEEGA, the mean (coefficient of variation [CV%]) $C_{\max,ss}$ was 831 ng/mL (32%) and $AUC_{0-24h,ss}$ was 13,616 ng·h/mL (36%). The accumulation ratio following daily administration of AKEEGA was 3.5-, and 2.6-fold for niraparib AUC_{0-24h} and $C_{\max}$.

Niraparib exhibits dose proportional increase in $C_{\max}$ and AUC in the dose range of 30 mg (0.15 times the recommended dosage) to 400 mg (2 times the recommended dosage).

Abiraterone Acetate

Following the administration of AKEEGA, the mean (CV%) $C_{\max,ss}$ was 151 ng/mL (59%) and $AUC_{0-24h,ss}$ was 707 ng·h/mL (59%) for abiraterone. The accumulation ratio following daily administration of AKEEGA was 2-, and 1.8-fold for abiraterone AUC_{0-24h} and $C_{\max}$.

No major deviation from dose proportionality was observed for abiraterone acetate in the dose range of 250 mg (0.25 times the recommended dosage) to 1,000 mg (the recommended dosage).

Absorption

Niraparib

The median $T_{\max}$ was 3 hours after dosing. The absolute bioavailability of niraparib is approximately 73%.

Abiraterone Acetate

The median $T_{\max}$ of abiraterone was 1.5 hours after dosing.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold ($C_{\max}$) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in increased and highly variable exposures.

Distribution

Niraparib

The apparent volume of distribution of niraparib was 1,117 L. Niraparib is 83% bound to human plasma proteins.

Abiraterone Acetate

The apparent volume of distribution of abiraterone was 25,774 L. Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein.

Elimination

Niraparib

The mean $t_{1/2}$ of niraparib when given in combination was approximately 62 hours (CV%: 42%) and apparent CL/F was 16.7 L/h (CV%: 27%).

Abiraterone Acetate

The mean $t_{1/2}$ of abiraterone when given in combination was approximately 20 hours (CV%: 7.8%) and apparent CL/F was 1673 L/h (CV%: 24%).

Metabolism

Niraparib

Niraparib is metabolized by carboxylesterases.

Abiraterone Acetate

Abiraterone acetate is rapidly converted *in vivo* to abiraterone. CYP3A4 and SULT2A1 are the enzymes involved in the metabolism of abiraterone.

Excretion

Niraparib

About 48% (33% to 60%) of the radiolabeled dose was recovered in urine and 39% (28% to 47%) in feces. Unchanged niraparib accounted for 11% and 19% of the administered dose recovered in urine and feces, respectively.

Abiraterone Acetate

Approximately 88% of the radiolabeled dose is recovered in feces and 5% in urine. Unchanged abiraterone acetate and abiraterone accounted for 55% and 22% of the administered dose recovered in the feces, respectively.

Specific Populations

No clinically significant effects on the PK of niraparib and abiraterone were observed based on body weight (43.3-165 kg for niraparib and 46-165 kg for abiraterone), age (45-90 years for niraparib and 43-90 years for abiraterone), race/ethnicity (White, Asian, and Hispanic) and mild to moderate renal impairment (CLcr: 30-90 mL/min). Severe renal impairment (CLcr: 15-30 mL/min) has not been studied.

Hepatic Impairment

Niraparib

Mild hepatic impairment did not affect the exposure of niraparib. Moderate hepatic impairment (Total bilirubin > 1.5 to 3 x ULN and any aspartate aminotransferase value) increased niraparib AUC by 56% compared to that of patients with normal hepatic function.

Abiraterone Acetate

Mild (Child-Pugh score of 5 to 6; Child-Turcotte-Pugh Class A) hepatic impairment increased abiraterone (AUC) by 1.1-fold and moderate (Child-Pugh score of 7 to 9; Child-Turcotte-Pugh Class B) hepatic impairment increased abiraterone (AUC) by 3.6-fold compared to subjects with normal hepatic function.

Severe (Child-Pugh score of 10 to 15; Child-Turcotte-Pugh Class C) hepatic impairment increased abiraterone AUC by 7-fold and the fraction of free drug increased by 2-fold in subjects compared to subjects with normal hepatic function.

Drug Interactions Studies

Niraparib

In Vitro Studies

- *Inhibition of Cytochrome P450 (CYP) Enzymes:* Niraparib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.
- *Induction of CYP Enzymes:* Niraparib is not a CYP3A4 inducer. Niraparib induces CYP1A2 *in vitro*.
- *Inhibition of Uridine 5'-Diphospho-Glucuronosyltransferases (UGTs):* Niraparib did not inhibit UGT1A1, UGT1A4, UGT1A9, and UGT2B7.
- *Inhibition of Transporter Systems:* Niraparib inhibits BCRP, but does not inhibit P-gp, BSEP, or MRP2.

Niraparib inhibits MATE 1 and 2.
- *Substrate of Transporter Systems:* Niraparib is a substrate of P-gp and BCRP. Niraparib is not a substrate of BSEP, MRP2, or MATE1 or 2.

Abiraterone Acetate

Clinical Studies

- *Effect of Strong CYP3A4 Inducers on Abiraterone:* Coadministration of rifampin (strong CYP3A4 inhibitor) decreased abiraterone mean AUC by 55%.
- *Effect of Strong CYP3A4 Inhibitors on Abiraterone:* Coadministration of ketoconazole (strong CYP3A4 inhibitor) had no clinically meaningful effect on the pharmacokinetics of abiraterone.
- *Effect of Abiraterone Acetate on CYP2D6 Substrates:* The C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone). The AUC for dextrophan, the active metabolite of dextromethorphan, increased approximately 1.3-fold.

- *Effect of Abiraterone Acetate on CYP1A2 Substrates:* When abiraterone acetate (plus prednisone) was given with a single dose of 100 mg theophylline (CYP1A2 substrate), no increase in systemic exposure of theophylline was observed.
- *Effect of Abiraterone Acetate on CYP2C8 Substrates:* The AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given to healthy subjects with a single dose of abiraterone acetate.

In vitro Studies

- *Cytochrome P450 (CYP) Enzymes:* Abiraterone is a substrate of CYP3A4 and has the potential to inhibit CYP1A2, CYP2D6, CYP2C8 and to a lesser extent CYP2C9, CYP2C19 and CYP3A4/5.
- *Transporter Systems:* Abiraterone acetate and abiraterone are not substrates of P-gp. Abiraterone acetate is an inhibitor of P-gp. Abiraterone and its major metabolites were inhibitors of OATP1B1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Niraparib

Carcinogenicity studies have not been conducted with niraparib.

Niraparib was clastogenic in an *in vitro* mammalian chromosomal aberration assay and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans. Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test.

Fertility studies in animals have not been conducted with niraparib. In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed at doses ≥ 10 mg/kg and ≥ 1.5 mg/kg in rats and dogs, respectively. These dose levels resulted in systemic exposures approximately 0.5 and 0.02 times, respectively, the human exposure (AUC_{0-24h}) at the dose of 200 mg daily. There was a trend toward reversibility of these findings 4 weeks after dosing was stopped.

Abiraterone Acetate

A two-year carcinogenicity study was conducted in rats at oral abiraterone acetate doses of 5, 15, and 50 mg/kg/day for males and 15, 50, and 150 mg/kg/day for females. Abiraterone acetate increased the combined incidence of interstitial cell adenomas and carcinomas in the testes at all dose levels tested. This finding is considered to be related to the pharmacological activity of abiraterone. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Abiraterone acetate was not carcinogenic in female rats at exposure levels up to

0.8 times the human clinical exposure (1,000 mg daily) based on AUC. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse.

Abiraterone acetate and abiraterone were not mutagenic in an *in vitro* microbial mutagenesis (Ames) assay or clastogenic in an *in vitro* cytogenetic assay using primary human lymphocytes or an *in vivo* rat micronucleus assay.

In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥ 50 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans at 1,000 mg daily.

In a fertility study in male rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in animals dosed for 4 weeks at ≥ 30 mg/kg/day orally. Mating of untreated females with males that received 30 mg/kg/day oral abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration.

In a fertility study in female rats, animals dosed orally for 2 weeks until day 7 of pregnancy at ≥ 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration.

The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1,000 mg/day based on body surface area.

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate.

13.2 Animal Toxicology and/or Pharmacology

Niraparib

In vitro, niraparib bound to DAT, NET, and SERT and inhibited uptake of norepinephrine and dopamine in cells with IC₅₀ values that were lower than the C_{min} at steady-state in patients receiving the 200 mg dose. Niraparib has the potential to cause effects in patients related to inhibition of these transporters (e.g., cardiovascular, central nervous system). Intravenous administration of niraparib to vagotomized dogs over 30 minutes at 1, 3, and 10 mg/kg resulted in an increased range of arterial pressures of 13% to 20%, 18% to 27%, and 19% to 25%, respectively, and increased range of heart rates of 2% to 11%, 4% to 17%, and 12% to 21%, respectively, above pre-dose levels. The unbound plasma concentrations of niraparib in dogs at these dose levels were

approximately 1.2, 3.9, and 15.5 times the unbound $C_{\max}$ at steady state in patients receiving the 200 mg dose.

In addition, niraparib crossed the blood-brain barrier in rats and monkeys following oral administration. The cerebrospinal fluid plasma $C_{\max}$ ratios of niraparib administered at 10 mg/kg orally to two rhesus monkeys were 0.10 and 0.52.

Abiraterone Acetate

A dose-dependent increase in cataracts was observed in rats after daily oral abiraterone acetate administration for 26 weeks starting at ≥ 50 mg/kg/day (similar to the human clinical exposure (AUC) at 1,000 mg dose daily). In a 39-week monkey study with daily oral abiraterone acetate administration, no cataracts were observed at higher doses (2 times greater than the clinical exposure (AUC) at 1,000 mg dose daily).

14 CLINICAL STUDIES

14.1 *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The efficacy of AKEEGA was investigated in Cohort 1 of MAGNITUDE (NCT03748641), a randomized double-blind, placebo-controlled, multi-cohort, multi-center study in which 423 patients with homologous recombination repair (HRR) gene-mutated (HRRm) mCRPC were randomized (1:1) to receive niraparib 200 mg and abiraterone 1,000 mg (N=212) or placebo and abiraterone (N=211) until unacceptable toxicity or progression. All patients received prednisone 10 mg daily and a GnRH analog or had prior bilateral orchiectomy. Patients with mCRPC who had not received prior systemic therapy in the mCRPC setting except for a short duration of prior abiraterone acetate plus prednisone (up to four months) and ongoing ADT, were eligible. Patients could have received prior docetaxel or androgen-receptor (AR) targeted therapies in either the metastatic castration-sensitive prostate cancer (mCSPC) or non-metastatic castration-resistant prostate cancer (nmCRPC) setting.

Randomization was stratified by prior docetaxel for mCSPC (yes or no), prior AR targeted therapy for mCSPC or nmCRPC (yes or no), prior abiraterone acetate for mCRPC (yes or no), and *BRCA*-status (*BRCA*m vs. other).

Of the 423 patients enrolled, 225 (53%) had *BRCA* gene mutations (*BRCA*m). Mutation status of *BRCA* genes was determined prospectively using the Foundation One CDx tissue assay or other clinical trial assays.

Among the 225 patients with *BRCA*m, the median age was 68 years (range 43-100) and 66% were 65 years of age or older; 72% were White, 17% Asian, and 1% Black, and 10% other or not reported; 12% were Hispanic or Latino; and baseline ECOG performance status (PS) was 0 (66%) or 1 (34%). Twenty-four percent had received prior docetaxel, 5% received prior AR-targeted therapy for mCSPC or nmCRPC, and 26% received prior abiraterone acetate plus prednisone for up to 4 months for mCRPC. Thirty-seven percent had bone-only metastases and 21% had visceral metastases. Seven percent had *BRCA1* mutations, 78% had *BRCA2* mutations, and 15% had *BRCA* mutations in combination with mutations in other HRR genes.

The major efficacy outcome measure was radiographic progression free survival (rPFS) determined by blinded independent central radiology (BICR) review evaluated per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (soft tissue lesions) and Prostate Cancer Working Group-3 (PCWG-3) criteria (bone lesions). Overall survival (OS) was an additional efficacy outcome measure.

A statistically significant improvement in rPFS for niraparib plus abiraterone compared to placebo plus abiraterone was observed in *BRCAm* patients, and the Cohort 1 intention to treat (ITT) population. In an exploratory analysis in the subgroup of 198 (47%) patients with non-*BRCa* mutations, the rPFS hazard ratio was 0.99 (95% CI: 0.67, 1.44) and the OS hazard ratio was 1.13 (95% CI: 0.77, 1.64), indicating that the improvement in the ITT population was primarily attributed to the results seen in the subgroup of patients with *BRCAm*.

The efficacy results are presented in Table 4 and Figures 1 and 2 for patients in Cohort 1 with *BRCA* mutations.

Table 4: Efficacy Results from the *BRCAm* Subgroup of the MAGNITUDE Study

Endpoints	AKEEGA (N=113)	Placebo (N=112)
Radiographic Progression-free Survival^a		
Event of disease progression or death (%)	45 (40%)	64 (57%)
Median, months (95% CI)	16.6 (13.9, NE)	10.9 (8.3, 13.8)
Hazard Ratio ^b (95% CI)	0.53 (0.36, 0.79)	
p-value ^c	0.0014	

^a rPFS results based on blinded independent central review at primary analysis.

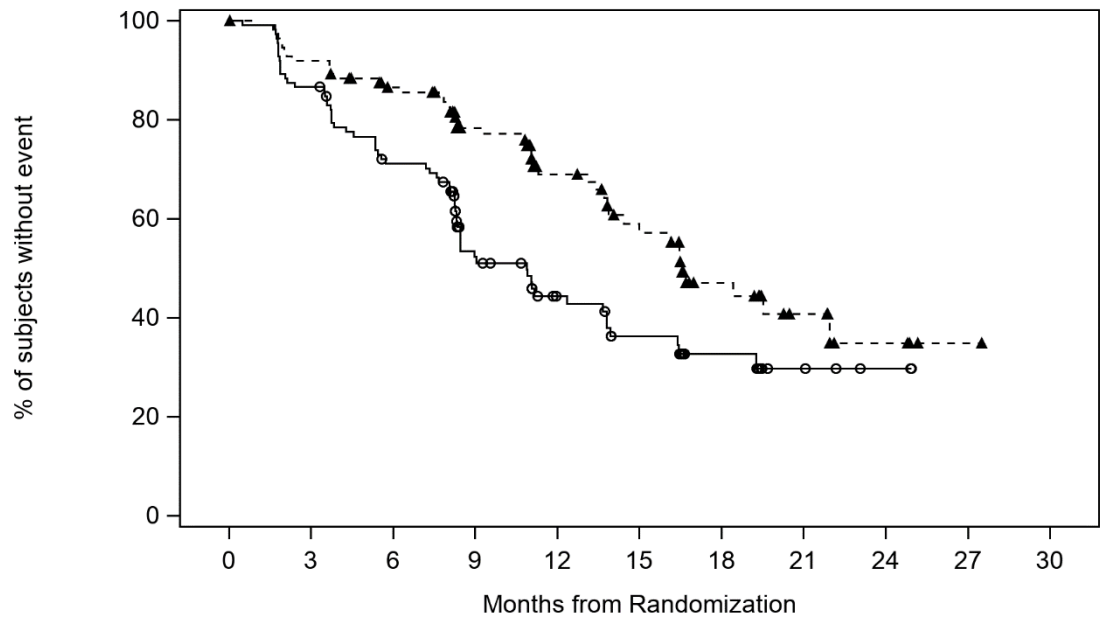
^b Cox proportional hazards model stratified by prior docetaxel (yes vs. no) and prior abiraterone (yes vs. no).

^c Stratified log-rank test two-sided p-value

NE = not estimable

At the protocol pre-specified final OS analysis in Cohort 1, 60 (53%) deaths and 70 (63%) deaths were observed in the AKEEGA arm and placebo arm, respectively, for patients with *BRCAm*. In an exploratory OS analysis in the subgroup of patients with *BRCAm*, the median in the AKEEGA arm was 30.4 (95% CI: 27.6, NE) and 28.6 months (95% CI: 23.8, 33.0) in the placebo arm, with an OS hazard ratio of 0.79 (95% CI: 0.55, 1.12).

Figure 1: Kaplan-Meier Plot of BICR Assessed Radiographic Progression-Free Survival in the *BRCAm* Population (MAGNITUDE, primary analysis)

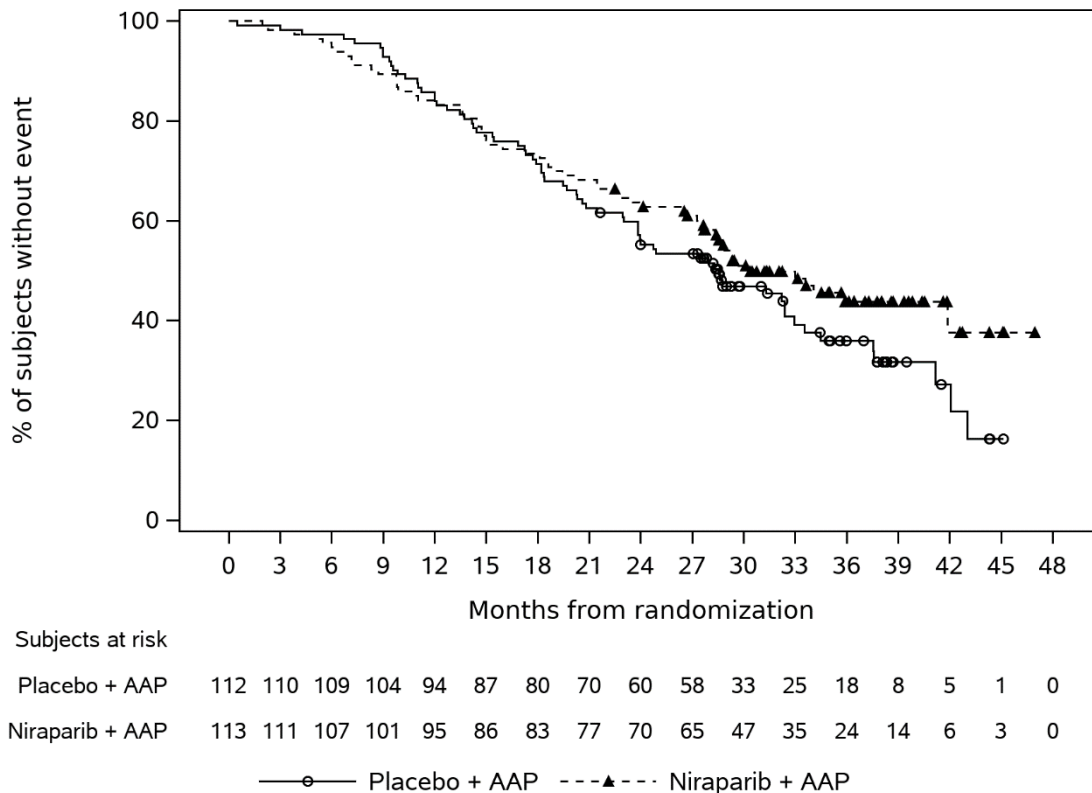


Subjects at risk

Placebo + AAP	112	97	77	43	28	20	11	5	2	0	0
Niraparib + AAP	113	103	90	65	45	31	18	9	4	1	0

—○— Placebo + AAP - - -▲- - - Niraparib + AAP

Figure 2: Kaplan-Meier Plot of Overall Survival in the *BRCAm* Population (MAGNITUDE, final analysis)



16 HOW SUPPLIED/STORAGE AND HANDLING

AKEEGATM (niraparib and abiraterone acetate) tablets are available in the strengths and packages listed below:

- AKEEGA 50 mg/500 mg film-coated tablets

Yellowish orange to yellowish brown, oval, film-coated tablets debossed with “N 50 A” on one side and plain on the other side. They are available in bottles of 60 tablets.
NDC 57894-050-60
- AKEEGA 100 mg/500 mg film-coated tablets

Orange, oval, film-coated tablets debossed with “N 100 A” on one side and plain on the other side. They are available in bottles of 60 tablets.
NDC 57894-100-60

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

Based on its mechanism of action, AKEEGA may harm a developing fetus. Females who are or may become pregnant should handle AKEEGA tablets with protection, e.g., gloves [see *Use in Specific Populations* (8.1)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hematologic Adverse Reactions

- Advise patients that periodic monitoring of their blood counts is recommended. Advise patients to contact their healthcare provider for new onset of pallor, weakness, dyspnea, fatigue, bleeding, fever, or symptoms of infection [see *Warnings and Precautions* (5.1, 5.2)].

Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions

- Inform patients that AKEEGA is associated with, hypokalemia that may lead to QT prolongation. Advise patients that hypertension, hypokalemia, and fluid retention will be monitored at least weekly for the first two months, then once a month. Advise patients to adhere to corticosteroids and to report symptoms of hypokalemia or edema to their healthcare provider [see *Warnings and Precautions* (5.3)].

Hepatotoxicity and Hepatic Impairment

- Inform patients that AKEEGA is associated with severe hepatotoxicity. Inform patients that their liver function will be monitored using blood tests. Advise patients to immediately report symptoms of hepatotoxicity to their healthcare provider [see *Warnings and Precautions* (5.4)].

Adrenocortical Insufficiency

- Inform patients that AKEEGA with prednisone is associated with adrenal insufficiency. Advise patients to report symptoms of adrenocortical insufficiency to their healthcare provider [see *Warnings and Precautions* (5.5)].

Hypoglycemia

- Inform patients that AKEEGA is associated with hypoglycemia. Advise patients with diabetes to monitor blood glucose during and after discontinuation of treatment with AKEEGA [see *Warnings and Precautions* (5.6)].

Posterior Reversible Encephalopathy Syndrome

- Inform patients that they are at risk of developing posterior reversible encephalopathy syndrome (PRES) that can present with signs and symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms [see *Warnings and Precautions* (5.8)].

Dosage and Administration

- Inform patients that AKEEGA is taken orally once daily with prednisone daily (according to their healthcare provider's instructions) and to not interrupt or stop either of these medications without consulting their healthcare provider [*see Dosage and Administration (2.2)*].
- Inform patients coadministered a gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with AKEEGA [*see Dosage and Administration (2.2)*].
- Inform patients that in the event of a missed daily dose of AKEEGA, they should take their normal dose as soon as possible on the same day and resume their next dose at the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [*see Dosage and Administration (2.2)*].
- Instruct patients to take AKEEGA tablets as a single dose once daily on an **empty stomach**. Instruct patients to not eat food 2 hours before and 1 hour after taking AKEEGA. AKEEGA taken with food causes increased exposure and may result in adverse reactions. Instruct patients to swallow tablets whole with water and not to break, crush, or chew the tablets [*see Dosage and Administration (2.2)*].

Embryo-Fetal Toxicity

- Inform patients that AKEEGA may harm a developing fetus and can cause loss of pregnancy [*see Warnings & Precautions (5.9) and Use in Specific Populations (8.1)*].
- Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of AKEEGA [*see Use in Specific Populations (8.3)*].
- Advise females who are pregnant or may become pregnant to handle AKEEGA tablets with protection, e.g., gloves [*see Use in Specific Populations (8.1) and How Supplied/Storage and Handling (16)*].

Infertility

- Advise male patients that AKEEGA may impair fertility [*see Use in Specific Populations (8.3)*].

Product of France

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044, USA

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PATIENT INFORMATION
AKEEGA™ (a kee' gah)
(niraparib and abiraterone acetate)
tablets

What is the most important information I should know about AKEEGA?

AKEEGA may cause serious side effects including:

- **Bone marrow problems called myelodysplastic syndrome (MDS) or a type of cancer of the blood called acute myeloid leukemia (AML).** MDS or AML that may lead to death has happened in people treated with niraparib, one of the medicines in AKEEGA. If you develop MDS or AML, your healthcare provider will stop treatment with AKEEGA.

Symptoms of low blood cell counts (low red blood cells, low white blood cells, and low platelets) are common during treatment with AKEEGA but can also be a sign of serious bone marrow problems, including MDS and AML. Tell your healthcare provider if you have any of the following symptoms during treatment with AKEEGA:

- | | |
|------------------------------------|---------------------------|
| ○ pale skin | ○ fever |
| ○ weakness | ○ frequent infections |
| ○ shortness of breath | ○ blood in urine or stool |
| ○ feeling tired | ○ weight loss |
| ○ bruising or bleeding more easily | |

Your healthcare provider will do blood tests to check your blood cell counts:

- weekly during the first month of treatment,
- every 2 weeks for the next 2 months of treatment,
- monthly for the remainder of the year,
- then every other month and as needed during treatment with AKEEGA.

See “What are the possible side effects of AKEEGA?” for more information about side effects.

What is AKEEGA?

AKEEGA is a prescription medicine used with prednisone to treat adults with prostate cancer:

- who have a certain type of abnormal *BRCA* gene, **and**
- whose prostate cancer has spread to other parts of the body and no longer responds to medical or surgical treatment that lowers testosterone (metastatic castration-resistant prostate cancer).

Your healthcare provider will perform a test to make sure AKEEGA is right for you.

It is not known if AKEEGA is safe and effective in females.

It is not known if AKEEGA is safe and effective in children.

Before taking AKEEGA, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure or heart problems
- have low blood potassium levels
- have liver or kidney problems
- have a history of adrenal problems
- have diabetes
- are receiving any other treatment for prostate cancer
- are pregnant or plan to become pregnant. AKEEGA can cause harm to your unborn baby and loss of pregnancy (miscarriage). Females who are or may become pregnant should handle AKEEGA tablets with protection, such as gloves.
- have a partner who is pregnant or may become pregnant. Males with female partners who are able to become pregnant should use effective birth control (contraception) during treatment and for 4 months after the last dose of AKEEGA.
- are breastfeeding or plan to breastfeed. It is not known if AKEEGA passes into your breastmilk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. AKEEGA may affect the way other medicines work, and other medicines may affect how AKEEGA works.

How should I take AKEEGA?

- Take AKEEGA and prednisone exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with AKEEGA if you have certain side effects.
- **Do not change or stop taking your prescribed dose of AKEEGA or prednisone without talking with your healthcare provider first.**
- Take your prescribed dose of AKEEGA 1 time a day.
- Take AKEEGA on an **empty stomach. Do not eat food 2 hours before and 1 hour after taking AKEEGA.** Taking AKEEGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- Swallow AKEEGA tablets whole with water. Do not break, crush, or chew tablets.
- If you miss a dose of AKEEGA, take the dose as soon as possible on the same day. Return to your normal schedule on the following day. Do not take extra tablets to make up the missed dose.
- You should start or continue a gonadotropin-releasing hormone (GnRH) analog therapy during your treatment with AKEEGA unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you take too much AKEEGA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of AKEEGA?

AKEEGA may cause serious side effects, including:

- **See “What is the most important information I should know about AKEEGA?”**
- **Low blood potassium levels (hypokalemia), fluid retention (edema), high blood pressure (hypertension) and heart problems.** To decrease the chance of this happening, you must take prednisone with AKEEGA exactly as your healthcare provider tells you. Your healthcare provider will check your blood pressure, do blood tests to check your potassium levels, and check for any signs and symptoms of fluid retention at least weekly for the first 2 months of treatment, then 1 time a month during treatment with AKEEGA. Tell your healthcare provider if you have any of the following symptoms:
 - dizziness
 - fast or irregular heartbeats
 - feel faint or lightheaded
 - headache
 - confusion
 - muscle weakness
 - pain in your legs
 - swelling in your hands, ankles, legs or feet
- **Liver problems.** Severe liver problems, liver failure and death has happened in people treated with abiraterone acetate, one of the medicines in AKEEGA. Your healthcare provider will do blood tests to check your liver function before starting treatment with AKEEGA, every 2 weeks for the first 3 months of treatment, and then monthly thereafter during treatment with AKEEGA. Tell your healthcare provider right away if you develop any symptoms of liver problems, including:
 - yellowing of the skin or eyes
 - darkening of the urine
 - severe nausea or vomiting
- **Adrenal problems.** Adrenal problems may happen if you stop taking prednisone, get an infection, or are under stress. Tell your healthcare provider right away if you develop any symptoms of adrenal problems, including:
 - feeling tired
 - weakness
 - feeling dizzy or lightheaded
 - nausea or vomiting
 - weight loss
- **Low blood sugar (hypoglycemia).** AKEEGA may cause low blood sugar in people taking medicines for diabetes. Severe low blood sugar has happened in people who take certain medicines for diabetes and were treated with abiraterone acetate, one of the medicines in AKEEGA. You and your healthcare provider should check your blood sugar levels during treatment and after you stop treatment with AKEEGA. Your healthcare provider may need to

change the dose of your diabetes medicine to decrease your risk of low blood sugar. Tell your healthcare provider right away if you have any of the following signs or symptoms of low blood sugar, including:

- headache
- drowsiness
- weakness
- dizziness
- confusion
- irritability
- hunger
- fast heartbeat
- sweating
- feeling jittery

- **Increased risk of bone fracture and death** when abiraterone acetate, one of the medicines in AKEEGA, and prednisone or prednisolone is used in combination with a type of radiation called Radium 223 (Ra-223) dichloride. You should not receive treatment with Ra-223 dichloride for at least 5 days after your last dose of AKEEGA with prednisone. Tell your healthcare provider about any other treatments you are taking for prostate cancer.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** PRES is a condition that affects the brain and may happen during treatment with AKEEGA. If you have headache, vision changes, confusion, or seizure with or without high blood pressure, please contact your healthcare provider.

The most common side effects of AKEEGA include:

- | | | |
|--|---------------------------------------|------------------------------------|
| • muscle and bone pain | • swelling in your legs or feet | • bleeding |
| • tiredness | • shortness of breath | • urinary tract infection |
| • changes in liver function blood tests | • decreased appetite | • cough |
| • constipation | • vomiting | • trouble sleeping |
| • high blood pressure | • dizziness | • decreased weight |
| • nausea | • Coronavirus disease 2019 (COVID-19) | • irregular heartbeat (arrhythmia) |
| • changes in kidney function blood tests | • headache | • falls |
| • increased potassium level in the blood | • stomach area pain | • fever |
| • decreased potassium level in the blood | | |

AKEEGA may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of AKEEGA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AKEEGA?

- Store AKEEGA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep AKEEGA and all medicines out of the reach of children.

General information about the safe and effective use of AKEEGA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AKEEGA for a condition for which it was not prescribed. Do not give AKEEGA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about AKEEGA that is written for health professionals.

What are the ingredients in AKEEGA?

Active ingredients: niraparib tosylate and abiraterone acetate

Inactive ingredients:

Core tablet: colloidal anhydrous silica, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, sodium lauryl sulfate.

50 mg/500 mg film-coated tablets: The film-coating contains iron oxide black, iron oxide red, iron oxide yellow, sodium lauryl sulphate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide.

100 mg/500 mg film-coated tablets: The film-coating contains iron oxide red, iron oxide yellow, sodium lauryl sulphate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured for: Janssen Biotech, Inc., Horsham, PA 19044, USA

For patent information: www.janssenpatents.com

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For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to www.akeegahcp.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

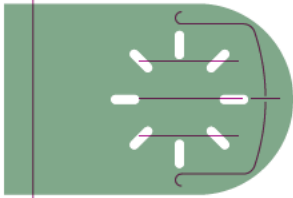
Issued: 8/2023

NDC 57894-050-98

Sample – Not for Sale

Akeega™
(niraparib and abiraterone acetate) tablets

50 mg / 500 mg
per tablet



TO CLOSE: Fold card and push back into sleeve firmly until locked.

Warning: Females who are or may become pregnant should handle AKEEGA tablets with protection, e.g., gloves (See Prescribing Information).

Rx only

Do not break, crush, or chew tablets

28 film-coated tablets — 14-Day Supply



Akeega™
(niraparib and abiraterone acetate) tablets

50 mg / 500 mg per tablet

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Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044, USA

Product of France

This package is child-resistant. Keep out of reach of children.

Store at room temperature 20°C to 25°C (68°F to 77°F);
excursions permitted to 15°C to 30°C (59°F to 86°F).

Recommended Dosage: See Prescribing Information.

Each film-coated tablet contains 50 mg niraparib (equivalent to 76.9 mg
niraparib tosylate) and 500 mg abiraterone acetate.

(niraparib and abiraterone acetate) tablets



50 mg / 500 mg
per tablet

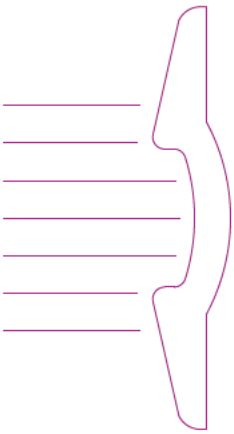
LOT
EXP



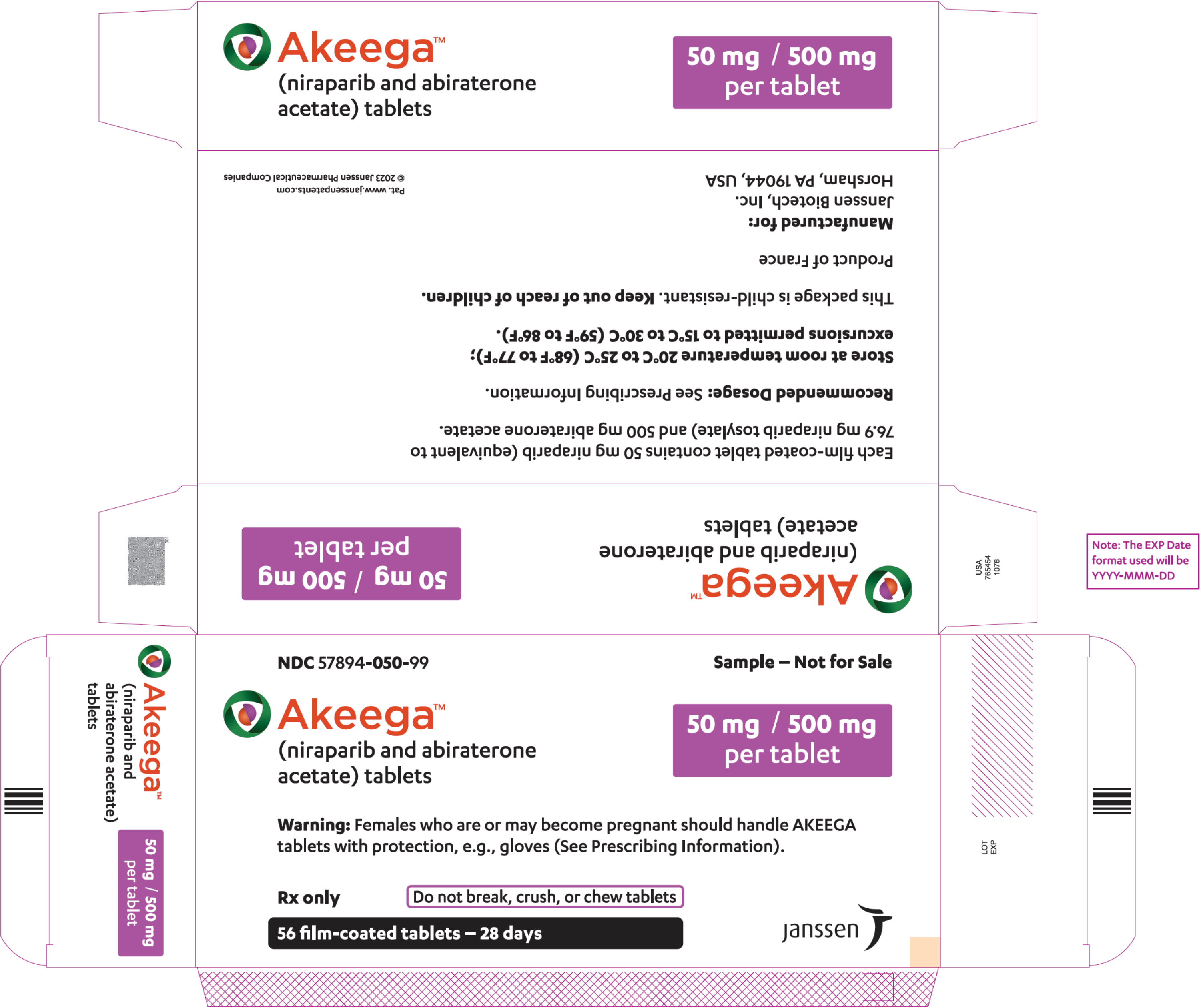
50 mg / 500 mg per tablet

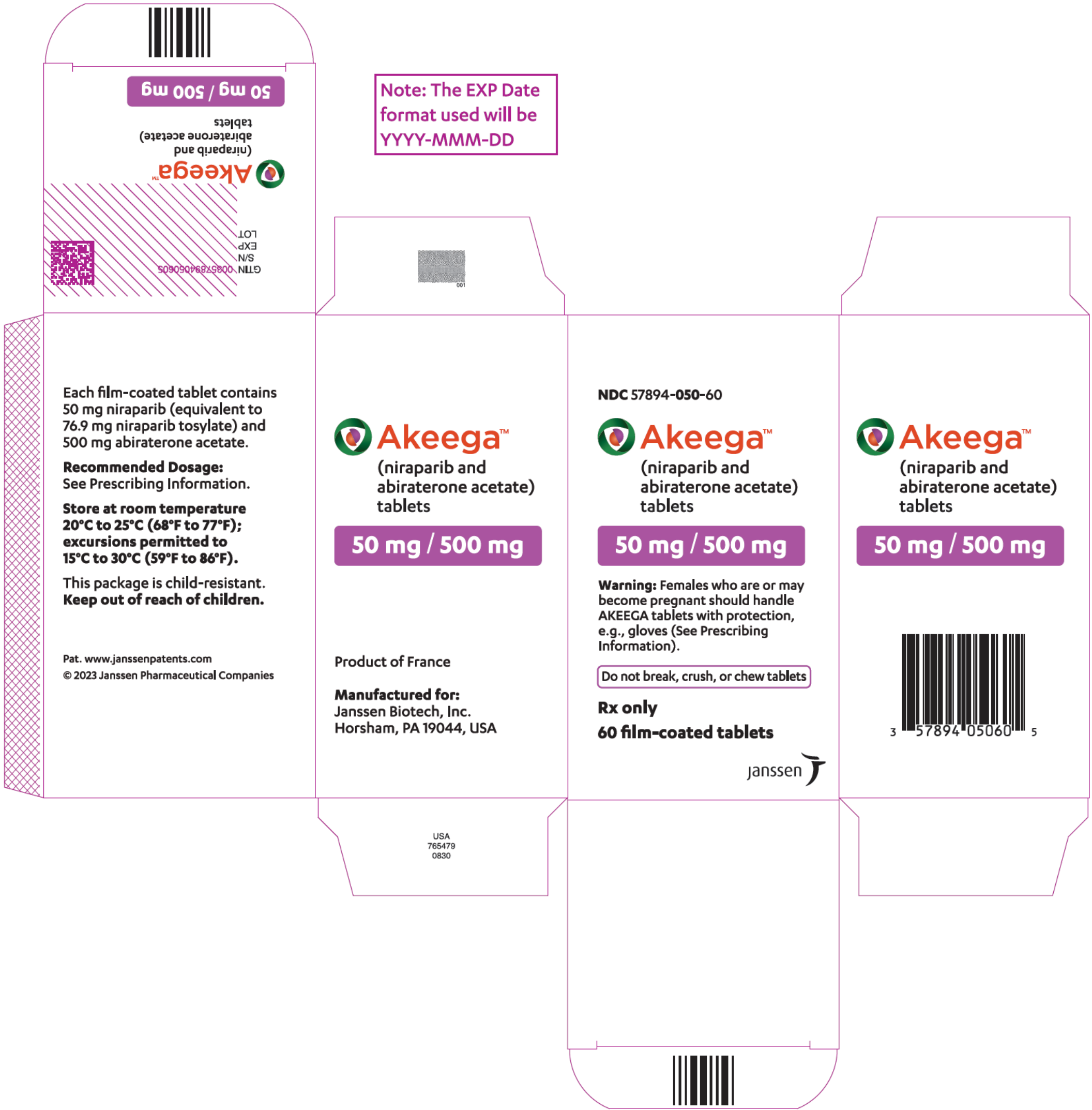


(niraparib and abiraterone acetate) tablets



(b) (4)





SENSI DI SVOLGIMENTO IN USO
PRESSO LA CARLUCCI SPA





3 57894 05060 5

Recommended Dosage:
See Prescribing Information.
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Do not break, crush, or chew tablets

NDC 57894-050-60

 **Akeega™**
(niraparib and abiraterone acetate) tablets

50 mg / 500 mg

Each film-coated tablet contains 50 mg niraparib (equivalent to 76.9 mg niraparib tosylate) and 500 mg abiraterone acetate.

Warning: Females who are or may become pregnant should handle AKEEGA tablets with protection, e.g., gloves (See Prescribing Information).

Rx only **60 film-coated tablets**



LOT
EXP

This package is child-resistant.
Keep out of reach of children.

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Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044, USA

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USA - 765641

Note: The EXP Date
format used will be
YYYY-MMM-DD

(b) (4)

NDC 57894-100-98

Sample – Not for Sale



Akeega™

(niraparib and abiraterone acetate) tablets

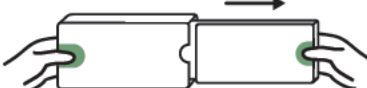
**100 mg / 500 mg
per tablet**



①



Press and hold



②

Pull out

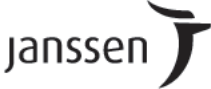
TO CLOSE: Fold card and push back into sleeve firmly until locked.

Warning: Females who are or may become pregnant should handle AKEEGA tablets with protection, e.g., gloves (See Prescribing Information).

Rx only

Do not break, crush, or chew tablets

28 film-coated tablets — 14-Day Supply



Akeega™

(niraparib and abiraterone acetate) tablets

100 mg / 500 mg per tablet

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USA - 765464



LOT

EXP

**100 mg / 500 mg
per tablet**

(niraparib and abiraterone acetate) tablets



Each film-coated tablet contains 100 mg niraparib (equivalent to 153.7 mg niraparib tosylate) and 500 mg abiraterone acetate.

Recommended Dosage: See Prescribing Information.

Store at room temperature 20°C to 25°C (68°F to 77°F);

excursions permitted to 15°C to 30°C (59°F to 86°F).

This package is child-resistant. **Keep out of reach of children.**

Product of France

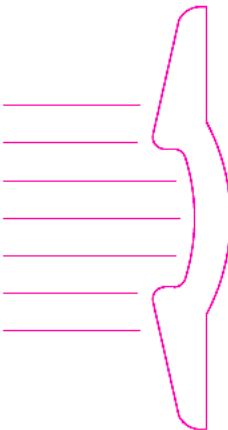
Manufactured for:

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Horsham, PA 19044, USA

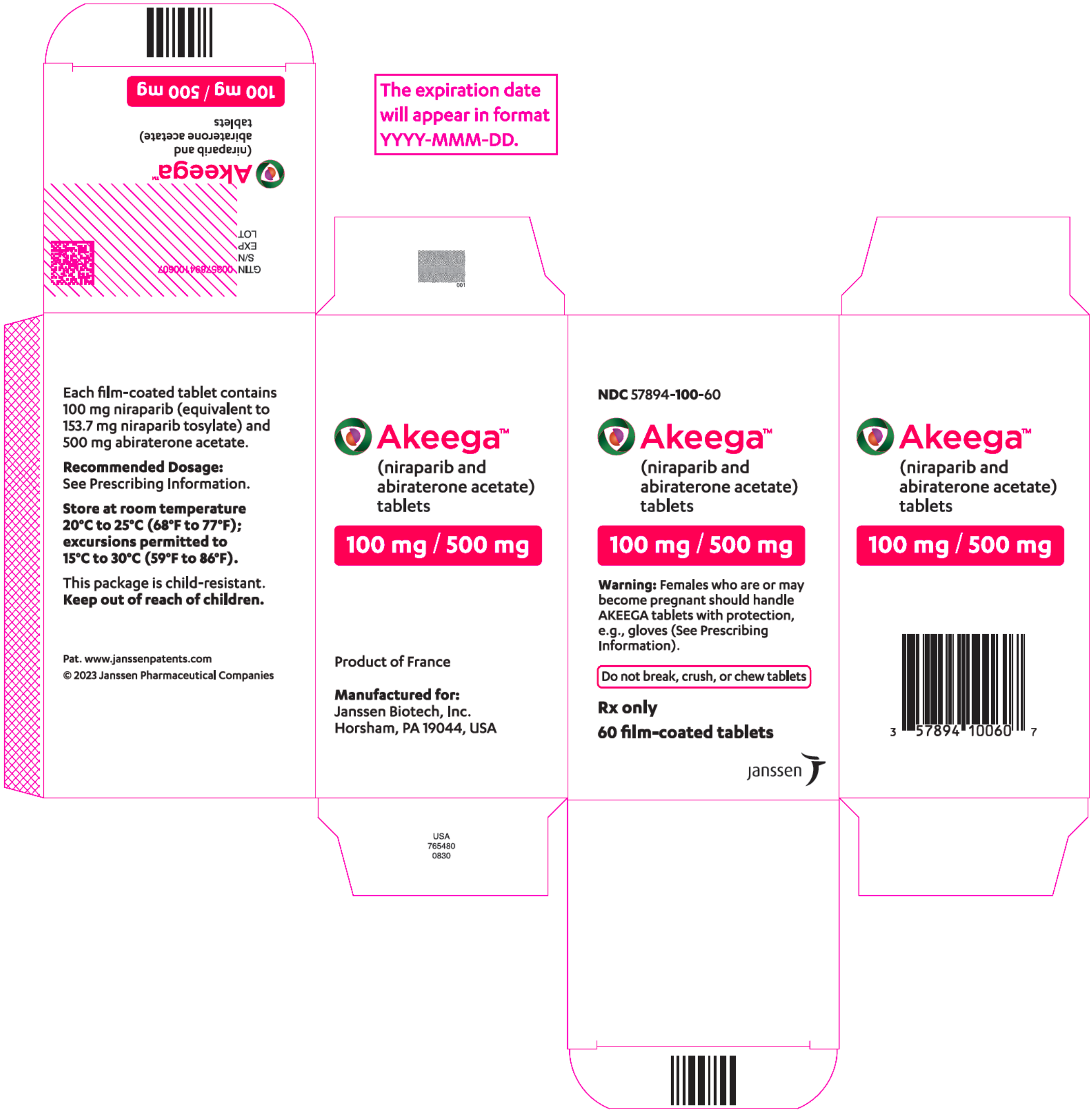
100 mg / 500 mg per tablet



(niraparib and abiraterone acetate) tablets

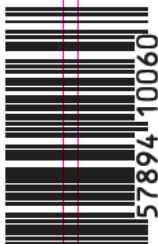


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SENSI DI SVOLGIMENTO IN USO
PRESSO LA CARLUCCI SPA





3 57894 10060 7

Recommended Dosage:
See Prescribing Information.
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Do not break, crush, or chew tablets

NDC 57894-100-60

 **Akeega™**
(niraparib and abiraterone acetate) tablets

100 mg / 500 mg

Each film-coated tablet contains 100 mg niraparib (equivalent to 153.7 mg niraparib tosylate) and 500 mg abiraterone acetate.

Warning: Females who are or may become pregnant should handle AKEEGA tablets with protection, e.g., gloves (See Prescribing Information).

Rx only **60 film-coated tablets**



This package is child-resistant.
Keep out of reach of children.

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LOT
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Note: The EXP Date
format used will be
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/s/

DANIEL L SUZMAN
08/11/2023 11:26:29 AM