Abemaxen

Abemaciclib INN

Everest

COMPOSITION

ABEMAXEN 150 Tablet: Each film coated tablet contains Abemaciclib INN 150 mg.
ABEMAXEN 200 Tablet: Each film coated tablet contains Abemaciclib INN 200 mg.

PHARMACOLOGY

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to Abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, Abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

INDICATION

Abemaciclib is indicated in:

- (HR)-positive, (HER2)-negative, node-positive, early breast cancer at high risk of recurrence in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant therapy.
- (HR)-positive, (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy.
- (HR)-positive (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant for with disease progression following endocrine therapy.
- HR-positive, HER2-negative advanced or metastatic breast cancer as monotherapy with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

DOSAGE AND ADMINISTRATION

In combination with fulvestrant, tamoxifen, or an aromatase inhibitor: 150 mg taken orally twice daily.

As monotherapy: 200 mg taken orally twice daily.

Pre/perimenopausal women and men treated with Abemaciclib plus an aromatase inhibitor or fulvestrant should also receive a GnRH agonist per clinical guidelines. In early breast cancer, continue Abemaciclib for 2 years or until recurrence/unacceptable toxicity. In advance or metastatic breast cancer, continue until progression or unacceptable toxicity. Abemaciclib may be taken with or without food.

Dose Modification

The recommended Abemaciclib dose modifications for adverse reactions are provided below. Discontinue Abemaciclib for patients unable to tolerate 50 mg twice daily.

Abemaciclib Dose Modification for Adverse Reactions

Dose Level	Abemaciclib Dose Combination with Fulvestrant, Tamoxifen, or an Aromatase Inhibitor	Abemaciclib Dose for Monotherapy
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	not applicable	50 mg twice daily

Hematologic toxicity
Grade 1–2: No dose modification is required.
Grade 3: Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Recurrent Grade 3 / Grade 4: Suspend dose until toxicity resolves to ≤Grade 2.Resume at next lower dose.

Diarrhea
Grade 1: No dose modification is required.
Grade 2 >24h:If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution. No dose reduction is required.
Persistent Grade 2 / Grade 3–4: Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.

Hepatotoxicity
Grade 1–2: No dose modification is required.
Persistent Grade 2 / Grade 3: Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
ALT/AST >3×ULN + bilirubin >2×ULN, or Grade 4: Discontinue

ILD / Pneumonitis
Grade 1–2: No dose modification is required.
Persistent Grade 2: Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose.
Grade 3–4: Discontinue

Venous thromboembolism (VTE)
Early BC: Any grade → Hold, treat, resume when stable
Advanced BC: Grade 1–2: No dose modification is required. Grade 3–4: Hold, treat, resume when stable
Grade 3–4: Suspend dose and treat as clinically indicated. Resume when the patient is clinically stable.

Other toxicities
Grade 1–2: No change
Persistent Grade 2 / Grade 3–4: Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose.

Dose Modification with CYP3A Inhibitors

Avoid concomitant use of ketoconazole. For other strong CYP3A inhibitors, reduce Abemaciclib to 100 mg twice daily (50 mg if already reduced); restore prior dose 3–5 half-lives after discontinuation. With moderate inhibitors, monitor closely and reduce in 50 mg steps if required.

Dose Modification in Severe Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh C), reduce Abemaciclib dosing frequency to once daily.

CONTRAINDICATION

None

ADVERSE REACTION

The following adverse reactions are described elsewhere in the labeling:
diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

WARNINGS AND PRECAUTION

Diarrhea

Diarrhea is common with Abemaciclib (81–90%); Grade 3 occurred in up to 20%. Onset is usually within the first month (median 6–8 days).

Manage promptly with antidiarrheals, fluids, and medical advice. For Grade 3/4 or hospitalization, hold until ≤Grade 1, then resume at a lower dose.

Neutropenia
Neutropenia occurred in 37–46% of patients; Grade ≥3 in up to 32%. Median onset was ~1 month; duration 11–16 days. Febrile neutropenia was rare (<1%). Monitor CBC regularly. For Grade 3/4, interrupt, reduce, or delay dosing.

Interstitial Lung Disease (ILD) / Pneumonitis
ILD/pneumonitis occurred in ~3% of patients; rare fatal cases reported. Monitor for cough, dyspnea, or hypoxia and exclude other causes. Interrupt or reduce for persistent/recurrent Grade 2; permanently discontinue for Grade 3/4.

Hepatotoxicity
Grade ≥3 ALT (2–6%) and AST (2–3%) elevations occurred. Onset typically 2–6 months; resolution in ~2 weeks. Monitor LFTs regularly. For persistent Grade 2 or any Grade 3/4, interrupt, reduce, or discontinue.

Venous Thromboembolism (VTE)
VTE occurred in 2–5% of patients, including DVT, PE, and cerebral venous thrombosis; deaths have occurred. Monitor for symptoms. Interrupt treatment for any VTE in early breast cancer or for Grade 3/4 in advanced disease.

Embryo-Fetal Toxicity
Abemaciclib can cause fetal harm. Animal studies showed teratogenicity and low fetal weight at exposures similar to humans. Advise women of reproductive potential to use effective contraception during therapy and for 3 weeks after the last dose.

USE IN SPECIFIC POPULATIONS
Pregnancy
Abemaciclib can cause fetal harm based on animal studies and its mechanism of action; no human data are available. In rats, exposure during organogenesis caused decreased fetal weight and cardiovascular and skeletal malformations at levels similar to human exposure. Advise pregnant women of the potential risk to the fetus. The background risk of birth defects is 2–4% and miscarriage 15–20% in the general population.

Lactation
There are no data on the presence of Abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Abemaciclib, advise lactating women not to breastfeed during Abemaciclib treatment and for 3 weeks after the last dose.

Females and Males of Reproductive Potential
Abemaciclib can cause fetal harm; verify pregnancy status in females of reproductive potential before treatment. Advise females to use effective contraception during therapy and for 3 weeks after the last dose. Based on animal studies, Abemaciclib may impair fertility in males of reproductive potential.

Pediatric Use
The safety and efficacy of Abemaciclib in pediatric patients younger have not been established.

Hepatic Impairment
No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering Abemaciclib to patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment
No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of Abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

OVERDOSE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS
CYP3A Inhibitors
Strong and moderate CYP3A4 inhibitors increased the exposure of Abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole
Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of Abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors
In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Abemaciclib dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Abemaciclib dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Abemaciclib discontinues a strong CYP3A inhibitor, increase the Abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A Inhibitors
With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Abemaciclib dose in 50 mg decrements as demonstrated in dose modification, if necessary.

Strong and Moderate CYP3A Inducers
Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of Abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

PHARMACEUTICAL INFORMATION
Storage
Store below 30°C in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
ABEMAXEN 150 Tablet: Each HDPE container contains 60 tablets (Each film coated tablet contains Abemaciclib INN 150 mg), a silica gel desiccant and polyester coil with child resistant closure.

ABEMAXEN 200 Tablet: Each HDPE container contains 60 tablets (Each film coated tablet contains Abemaciclib INN 200 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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