IOWA | Health and Human Services

Iowa PDL New Drug Review

Proprietary Name: Hernexeos®
Common Name: zongertinib
PDL Category: Antineoplastic Agents

Pharmacology/Usage: Zongertinib, the active ingredient of Hernexeos®, is a kinase inhibitor of human epidermal growth factor receptor 2 (HER2). In vitro, zongertinib inhibited phosphorylation of HER2, downstream signaling of HER2, and proliferation of lung cancer cells harboring HER2 tyrosine kinase domain activating mutations.

Indication: For the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Hernexeos® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to starting treatment. In addition, advise females of reproductive potential to use effective contraception during Hernexeos® treatment and for 2 weeks after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 60mg.

Swallow tablets whole with water. Do not split, crush, or chew tablets.

Recommended Dosage: Select patients for treatment of unresectable or metastatic NSCLC based on the presence of HER2 (ERBB2) tyrosine kinase domain activating mutations in tumor specimens. Information on FDA-approved tests for HER2 (ERBB2) tyrosine kinase domain activating mutations is available at http://www.fda.gov/CompanionDiagnostics.

The recommended dosage is based on body weight:

- <90kg: 120mg.
- ≥90kg: 180mg.

Take Hernexeos® orally once daily with or without food until disease progression or unacceptable toxicity. If a dose is missed within 12 hours, take the dose. If a dose is missed by more than 12 hours, skip the missed dose and take the next scheduled dose. If a dose is vomited, do not take an additional dose. Take the next dose at the regularly scheduled time.

There are recommended dosage modifications for adverse reactions, such as hepatotoxicity, left ventricular dysfunction, interstitial lung disease/pneumonitis, diarrhea, or other adverse reactions. Refer to the prescribing information for additional information.

Drug Interactions: Zongertinib is a CYP3A substrate. Avoid concomitant use of Hernexeos® with strong CYP3A inducers. If concomitant use cannot be avoided, increase Hernexeos® dose as recommended per the prescribing information.

Zongertinib is a breast cancer resistance protein (BCRP) inhibitor. Avoid concomitant use of Hernexeos® with certain BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration cannot be avoided, monitor for increased adverse reactions and follow recommendations provided in the approved product labeling for the BCRP substrate. For other BCRP substrates, monitor for increased adverse reactions and adjust the dosages of those substrates as clinically appropriate.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Hernexeos®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included diarrhea (52%), nausea (24%), vomiting (15%), rash (32%), nail disorders (19%), fatigue (25%), cough (24%), dyspnea (15%), musculoskeletal pain (24%), and upper respiratory tract infections (21%).

Select laboratory abnormalities included lymphocytes decreased (52%), leukocytes decreased (43%), hemoglobin decreased (37%), activated partial thromboplastin time increased (25%), platelets decreased (23%), alanine aminotransferase increased (39%), aspartate aminotransferase increased (33%), lipase increased (30%), bilirubin increased (26%), triglycerides increased (26%), calcium decreased (25%), amylase increased (24%), sodium decreased (23%), creatinine kinase increased (22%), albumin decreased (21%), cholesterol increased (20%), alkaline phosphatase increased (20%), magnesium decreased (20%), and potassium decreased (20%).

Hernexeos® can cause severe and life-threatening hepatotoxicity, including drug induced liver injury. Monitor liver function tests including ALT, AST, and total bilirubin at baseline prior to administration of Hernexeos®, every 2 weeks during the first 12 weeks, and then monthly thereafter as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Interrupt, reduce the dose, or permanently discontinue Hernexeos® based on the severity of the adverse reaction.

Hernexeos® can cause severe left ventricular dysfunction. Left ventricular ejection fractions (LVEF) decrease occurred with anti-HER2 therapies, including Hernexeos®. Treatment with Hernexeos® has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to the start of treatment. Before starting Hernexeos®, assess LVEF and monitor at regular intervals during treatment and as clinically indicated. Interrupt, reduce the dose, or permanently discontinue Hernexeos® based on the severity of the adverse reaction.

Hernexeos® can cause severe and life-threatening interstitial lung disease (ILD)/pneumonitis. Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis. Interrupt, reduce the dose or permanently discontinue Hernexeos® based on severity of confirmed ILD/pneumonitis.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Boehringer Ingelheim Pharmaceuticals, Inc.

Analysis: The efficacy of Hernexeos® was assessed in Beamion LUNG-1, which was a single-arm, open-label, multicenter, multicohort trial. Eligible patients were required to have unresectable or metastatic NSCLC with HER2 (ERBB2) mutations. In addition, patients with stable brain metastases were eligible to enroll. Patients with a history of non-infectious ILD/pneumonitis were excluded.

Patients in the study (N=71) received Hernexeos® 120mg once daily until disease progression or unacceptable toxicity. The baseline characteristics of the efficacy population included patients with an age of 62 years (range 30 to 80), while 70% were female, 55% were Asian, 39% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 61% had an ECOG PS of 1, 65% had never smoked, 100% had metastatic disease, and 37% had brain metastases. The median number of prior therapies was 1 (range 1 to 10), while 100% had prior platinum therapy and 78% had prior treatment with anti-PD-1/PD-L1 antibody. Patients had not received previous treatment with HER2-targeted tyrosine kinase inhibitor (TKI) or HER2-targeted antibody-drug conjugate (ADC).

The main efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by blinded independent central review (BICR). Results are presented in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Hernexeos® (N=71)
Objective Response Rate (ORR), %	75%
Complete Response, %	6%
Partial Response, %	69%
Duration of Response (DOR)	N=53
Range, months	1.3+, 15+
DOR ≥6 months, %	58%

Among the 71 patients, 5 had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to Hernexeos® treatment. Based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria per BICR, responses were observed in 3 patients.

Hernexeos® was also assessed in 34 patients with unresectable or metastatic HER2 (ERBB2) TKD mutation-positive non-squamous NSCLC who had received previous treatment with platinum-based chemotherapy and a HER2-targeted ADC. Eligibility criteria were otherwise similar to the efficacy population described above. The median age was 58 years (range 31 to 85), while 65% were female, 50% were White, 21% had baseline ECOG performance status 0, 79% had ECOG performance status 1, 65% had never smoked, 100% had metastatic disease, and 74% had brain metastases. The median number of prior therapies was 3, with 100% having had prior platinum therapy and 77% had prior treatment with anti-PD-1/PD-L1 antibody. Furthermore, 2.9% had received previous treatment with a HER2-targeted TKI. Confirmed ORR by RECIST v1.1 based on BICR was 44%, with 2.9% of patients having a complete response. Median DOR was 5.4 months and 27% of responders had an observed DOR ≥6 months.

Place in Therapy: Hernexeos® is a kinase inhibitor indicated for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Select patients for treatment of unresectable or metastatic NSCLC based on the presence of HER2 (ERBB2) tyrosine kinase domain activating mutations in tumor specimens. Efficacy was assessed in a single-arm, open-label, multicenter, multicohort study that included patients required to have unresectable or metastatic NSCLC with HER2 (ERBB2) mutations. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR). The ORR for the included patients (N=71) was 75%, while the DOR ≥6 months was 58%.

Summary

It is recommended that Hernexeos® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Hernexeos [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2025.

Prepared By: Iowa Medicaid Date: 09/22/2025