Policy Type: PA/SP Pharmacy Coverage Policy: COMM339

Description

Zongertinib (Hernexeos) and sevabertinib (Hyrnuo) are orally administered human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors (TKIs).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zongertinib (Hernexeos)	Advanced or metastatic HER2-positive non-small cell lung cancer (NSCLC)	60mg tablet	Weight: <90kg: 60 tablets/30 days
			Weight: ≥90kg: 180 tablets/60 days
sevabertinib (Hyrnuo)		10mg tablet	120 tablets/30 days

Initial Evaluation

I. **Zongertinib (Hernexeos) or Sevabertinib (Hyrnuo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **non-small cell lung cancer (NSCLC); AND**
      1. The member has unresectable, locally advanced (Stage III), or metastatic (IV) disease; **AND**
      2. Confirmation of human epidermal growth factor receptor 2 (HER2) mutation; **AND**
      3. Confirmation of non-squamous histological subtype; **AND**
      4. The member has had disease progression on at least one line of systemic therapy (e.g., immune checkpoint inhibitor [e.g., nivolumab*, pembrolizumab*, etc.], platinum-based chemotherapy [e.g., cisplatin, carboplatin, etc.]), unless not tolerated or contraindicated.

*Please note: medications notated with an asterisk may require additional review.

II. Zongertinib (Hernexeos) and Sevabertinib (Hyrnuo) are considered investigational when used for all other conditions, including but not limited to:
   A. Zongertinib (Hernexeos) and sevavertinib (Hyrnuo) used in combination with another oncology therapy
   B. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)
   C. Solid tumors outside of NSCLC
   D. Squamous HER2 NSCLC

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

I. Zongertinib (Hernexeos) and sevabertinib (Hyrnuo) are human epidermal growth factor receptor (HER2) tyrosine kinase inhibitor (TKI), FDA-approved for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) with HER2 [ERBB2] tyrosine kinase domain activating mutations, who have received prior systemic therapy.
II. Both zongertinib (Hernexeos) and sevabertinib (Hyrnuo) were studied in clinical trials for HER2 NSCLC as monotherapy. At this time, there is insufficient evidence to support the efficacy and safety of either of these agents to be used in combination with other oncology therapies.
III. Numerous gene alterations have been identified in the setting of NSCLC that impact therapy selection. Testing of lung cancer specimens for these alterations is important for identification of potentially efficacious targeted therapies. The national comprehensive (NCCN) guidelines recommend establishing histologic subtypes via a biopsy and/or plasma testing in the setting of advanced or metastatic NSCLC.

Zongertinib (Hernexeos)

IV. Zongertinib (Hernexeos) was studied in a Phase 1, multicenter, multicohort, open-label, single-arm, study (LUNG-1). The study included a population of nonsquamous tyrosine kinase domain (TKD) mutant, HER2 NSCLC participants. Participants received zongertinib (Hernexeos) 120mg once daily until disease progression or unacceptable toxicity. Baseline characteristics included a median age of 58-62 years old, mostly female (65%-68%), stage IV disease (94-100%). The primary outcome was overall response rate (ORR) and secondary outcomes included median duration of response and progression free survival.
V. There were two key cohorts in the LUNG-1 study. Cohort 1 included 75 participants with non-squamous HER2 TKD mutant NSCLC who had previous platinum therapy (100%) and prior anti-PD-1/PD-L1 antibody (78%). No patient received previous HER2-targeted TKI or HER2-targeted ADC. Cohort 5 included 31 participants who had previous platinum therapy (100%), anti-PD-1/PD-L1 antibody (77%), HER2-targeted TKI (2.9%), and HER2-directed ADC's (10%). The primary outcome was overall response rate (ORR). Of the 75 participants in cohort one, 50 (67%) achieved a documented response [97.5% CI, 54-78] $p<0.001$ versus 15 (42%) 15, (42%) [95% CI, 26-59] $p =0.01$ in cohort five. Findings from the LUNG-1 study is low-quality, as results from single arm, open-label studies are considered to be observational. Overall response rate (ORR) is a surrogate marker that does not correlate with clinically significant outcomes, such as effects on morbidity or mortality, and additional confirmatory trials are required to fully evaluate for benefit of zongertinib (Hernexeos).

Sevabertinib (Hyrnuo)

VI. Sevabertinib (Hyrnuo) was studied in a Phase 1/2, multi-cohort, open-label, single-arm study (SOHO-1) in 209 participants with locally advanced or metastatic HER2 positive NSCLC in three separate cohorts. Participants who had at least one prior line of systemic therapy but no

previous treatment with HER2-directed therapy (cohort D, n=81), participants who had previous treatment with HER2-directed therapy (cohort E, n=55), and participants who were treatment-naïve (cohort F, n=73). Baseline characteristics included a median age of 60-65 years old, mostly female (62-65%), of Asian race (58-70%), and were diagnosed with non-squamous adenocarcinoma (95-100%). Cohort D included 25% that had previous platinum-based chemotherapy but no immunotherapy, 69% that had platinum-based chemotherapy and immunotherapy and 72% that had anti-PD-1/PD-L1 antibody therapy. Cohort E consisted of 75% participants with previous fam-trastuzumab deruxtecan (Enhertu) treatment and 25% participants with prior HER2-targeted ADC treatment. The primary outcome was overall response rate (ORR). Of the 81 participants treated with prior systemic therapy (cohort D), 52 (64%) achieved a documented response [95% CI, 53-75] p<0.001. ORR in the prior HER2-directed therapy group was 21 (38%) [95% CI, 25-52] and 52 (71%) [95% CI, 59-81] in the treatment-naïve group. Findings from the SOHO-1 study is of low-quality, as results from single arm, open-label studies are considered to be observational. Overall response rate (ORR) is a surrogate marker that does not correlate with clinically significant outcomes, such as effects on morbidity or mortality, and additional confirmatory trials are required to fully evaluate for benefit of sevabertinib (Hyrnuo).

VII. The National Comprehensive Cancer Network (NCCN) guidelines have been updated to provide a category 2A recommendation for treatment with zongertinib (Hernexeos) and sevabertinib (Hyrnuos) after progression on systemic therapy in locally advanced or metastatic HER2 NSCLC.

- First-line treatment for locally advanced or metastatic HER2 NSCLC includes systemic therapy with a systemic immune checkpoint inhibitor and platinum-based chemotherapy. Adenocarcinoma is representative of the nonsquamous NSCLC subtype:
    i. Adenocarcinoma: pembrolizumab/carboplatin/pemetrexed, pembrolizumab/cisplatin/pemetrexed, cemiplimab-rwlc/ pemetrexed /(carboplatin or cisplatin) (all category 1, preferred), atezolizumab/carboplatin/paclitaxel/bevacizumab, atezolizumab/carboplatin/albumin-bound paclitaxel, nivolumab/ipilmumab/ pemetrexed/(carboplatin or cisplatin), cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin), tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel, tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/ pemetrexed (all category 1, other recommended)

Investigational or Not Medically Necessary Uses

I. There are ongoing clinical studies to assess efficacy and safety of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in other settings. Zongertinib (Hernexeos) and sevabertinib (Hyrnuo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

A. zongertinib (Hernexeos) or sevabertinib (Hyrnuo) used in combination with another oncology therapy

i. Zongertinib (Hernexeos) and sevabertinib (Hyrnuo) are FDA-approved for monotherapy in the setting of HER2 NSCLC. National Comprehensive Cancer Network guidelines also recommend use of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) as monotherapy. There is currently a lack of scientific

studies evaluating the safety and efficacy of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in combination with other oncology therapy.

B. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)

i. There is currently a lack of scientific studies evaluating the safety and efficacy of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in NSCLC mutations outside of HER2. Thus, there is a lack of scientific evidence to support the treatment of NSCLC mutations outside of HER2.

C. Solid tumors outside of NSCLC

i. Human epidermal growth factor receptor 2 mutations have been observed in solid tumors (i.g. cervical cancers, skin cancers, breast cancer). Currently, there are no clinical trials evaluating the use of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in any other disease states outside of NSCLC. There is insufficient scientific evidence to support the use of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in the treatment of solid tumors with HER2 rearrangement.

D. Squamous HER2 NSCLC

i. Zongertinib (Hernexeos) and sevabertinib (Hyrnuo) are FDA-approved for non-squamous HER2 NSCLC. The National Comprehensive Cancer Network guideline does not provide distinguished recommendations based on histology for the treatment of HER2 NSCLC, however, evidence of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in squamous HER2 NSCLC (as defined by y squamous-cell carcinoma [NOS], squamous carcinoma, or small-cell nonkeratinizing squamous-cell carcinoma) is limited. The LUNG-1 studies did not include participants with squamous HER2 NSCLC. The SOHO-1 study did not exclude participants diagnosed with squamous histology, however, this group only consisted of six participants (<3%) of the total study population, leaving underrepresentation and thus insufficient evidence to support the use of these agents in HER2 NSCLC with a squamous histology. There is currently a lack of scientific studies evaluating the safety and efficacy of zongertinib (Hernexeos) and sevabertinib (Hyrnuo) in squamous NSCLC.

References

1. Hernexeos (zongertinib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2025.
2. Sevabertinib (Hyrnuo) [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc.; November 2025.
3. Heymach JV, Ruiter G, Ahn MJ, et al. Zongertinib in Previously Treated HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2025;392(23):2321-2333. doi:10.1056/NEJMoa2503704
4. Le X, Kim TM, Loong HH, et al. Sevabertinib in Advanced HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. Published online October 17, 2025. doi:10.1056/NEJMoa2511065Food and Drug Administration.
5. Food and Drug Administration. FDA grants accelerated approval to zongertinib for non-squamous NSCLC with HER2 TKD activating mutations. Updated August 08, 2025. Accessed August 08, 2025. FDA grants accelerated approval to zongertinib for non-squamous NSCLC with HER2 TKD activating mutations | FDA
6. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2026 – December 2, 2025). 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 2, 2025.
7. Food and Drug Administration. FDA grants accelerated approval to sevabertinib for non-squamous non-small cell lung cancer. Updated November 19, 2025. Accessed December 2, 2025. FDA grants accelerated approval to sevabertinib for non-squamous non-small cell lung cancer | FDA

Related Policies

There are currently no related disease policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2026