CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219972
PDUFA Goal Date	November 30, 2025
TTT #	2025-13913
Reviewer Name	Ingrid N. Chapman, PharmD, BCPS
Team Leader	Naomi Boston, PharmD
Division Director	Laura Zendel, PharmD
Review Completion Date	November 18, 2025
Subject	Evaluation of Need for a REMS
Established Name	Sevabertinib
Trade Name	Hyrnuo
Name of Applicant	Bayer Healthcare Pharmaceuticals, Inc
Therapeutic Class	kinase inhibitor
Dosage Form	10 mg tablets for oral administration
Dosing Regimen	20 mg orally twice daily for a total daily dose of 40 mg

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Hyrnuo (sevabertinib) is necessary to ensure the benefits outweigh its risks.

Bayer Healthcare Pharmaceuticals Inc. submitted a New Drug Application (NDA) 219972 for sevabertinib with the proposed indication: for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. HER2 and ERBB2 are used interchangeably and refer to human epidermal growth factor receptor 2 and erb-b2 receptor tyrosine kinase 2, respectively.

During the course of the review, the indication was revised to the following:
Hyrnuo is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This application was reviewed by the Division of Oncology 2 (DO2). The efficacy of sevabertinib was established in Study SOHO-01. Data from two groups, Group D and Group E, were used to establish efficacy. Among 70 subjects who had not received prior HER2-directed therapy (Group D), the objective response rate (ORR) per blinded independent central review (BICR) was 71% (95% CI: 59, 82) and the median duration of response (DOR) was 9.2 months (95% CI: 6.3, 15), with 54% of responders having an observed DOR ≥ 6 months and 18% of responders with an observed DOR ≥ 12 months. Among 52 subjects with locally advanced or metastatic, non-squamous NSCLC with HER2 tyrosine kinase domain (TKD) mutations who had received prior systemic treatment with platinum-based chemotherapy and a HER2-targeted ADC (Group E) the ORR was 38% (95% CI: 25, 53), with a median DOR of 7.0 months (95% CI: 5.6, NE) and 60% of responders having a DOR ≥ 6 months.

The serious risks associated with sevabertinib are diarrhea, hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of sevabertinib outweigh its risks. The FDA determined sevabertinib has an acceptable safety profile when assessed in the context of a life-threatening disease. FDA expects the labeling to be sufficient to communicate the risks of diarrhea, hepatotoxicity, interstitial disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity. FDA also expects the likely prescribers of sevabertinib (oncologists) to be familiar with managing these risks because other products they prescribe, including tyrosine kinase inhibitors, have similar risks.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Hyrnuo (sevabertinib) is necessary to ensure the benefits outweigh its risks. Bayer Healthcare Pharmaceuticals Inc. submitted a New Drug Application (NDA) 219972 for sevabertinib with the proposed indication: for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. HER2 and ERBB2 are used interchangeably and refer to human epidermal growth factor receptor 2 and erb-b2 receptor tyrosine kinase 2, respectively. This application was reviewed by the Division of Oncology 2 (DO2). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Hyrnuo (sevabertinib), a new molecular entity (NME),[a] is a reversible tyrosine kinase inhibitor (TKI) that targets mutant forms of HER2 as well as wildtype HER2. HER2 (ERBB2) is a receptor tyrosine kinase encoded by the ERBB2 proto-oncogene localized on the long arm of chromosome 17 (17q21) (Loeffler, 2023). Sevabertinib is proposed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.[b]

Sevabertinib is proposed as 10 mg tablets for oral administration. The recommended dosage is 20 mg (two 10 mg tablets) orally twice daily for a total daily dose of 40 mg. Treatment with sevabertinib is continued indefinitely or until unacceptable toxicity occurs.[c] Sevabertinib is not currently approved in any other jurisdiction.[b]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219972 relevant to this review:

- **03/28/2025**: Bayer Healthcare Pharmaceuticals Inc. submitted NDA 219972 to the FDA for the treatment of adult patients with advanced NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
- **08/07/2025**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that at this time, we do not anticipate the need for further risk mitigation strategies, such as a Boxed Warning or a REMS.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*
[b] Bayer Healthcare Pharmaceuticals, Inc. Hyrnuo (sevabertinib). NDA) 219972. Prescribing Information, proposed March 28, 2025.
[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Lung cancer (both small cell and non-small cell) is the second most common cancer in men and women (excluding skin cancer).[1] Lung cancer is the leading cause of cancer death in the U.S. accounting for 1 in 5 of all cancer deaths. In 2025, the American Cancer Society estimates approximately 226,650 (110,680 in men and 115,970 in women) new cases of lung cancer and about 124,730 (64,190 in men and 60,540 in women) deaths due to lung cancer.[d,e]

NSCLC represents 80-85% of all lung cancers and *HER2* gene mutations occur in approximately 1% to 4% of those NSCLC cases.[f] This mutation is more prevalent in those with adenocarcinoma and in non-smokers, Asian people, and women (Loeffler, 2023). These patients often develop central nervous system (CNS) disease, with brain metastases reported in up to 47% of patients.[g] The 5-year relative survival rate for patients with localized (67%), regional (40%), and distant (12%) NSCLC disease varies markedly, depending on the stage at diagnosis.[h] Median survival in patients with metastatic *HER2*-mutated NSCLC is 17 to 23 months.[f]

3.2. Description of Current Treatment Options

Treatment of NSCLC depends on the stage at diagnosis and may include surgery to remove the cancer (early-stage NSCLC) or a combination of surgery, chemotherapy, and radiation. Radiation and traditional chemotherapy often help to shrink the cancer prior to surgery. Radiofrequency ablation (RFA) is an option for those who are not healthy enough to undergo surgery.[i] People with NSCLC will typically undergo genetic testing to determine which targeted therapies are potential treatment options.

There are no drugs specifically targeting HER2-mutated NSCLC currently under traditional FDA-approval in the U.S. Treatments used for patients with HER2-mutated NSCLC are the same as those used for patients with NSCLC without a specific driver mutation to include platinum-based chemotherapy doublet with immune therapy. The following are examples of treatment regimens for NSCLC without a driver mutation (Lilenbaum, 2025):

- Non-squamous NSCLC: combination of cisplatin or carboplatin with pemetrexed and pembrolizumab

[d] American Cancer Society. Key Statistics for Lung Cancer. Accessed November 12, 2025. https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html
[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*
[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
[g] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.
[h] American Cancer Society. Lung Cancer Survival Rates. Accessed November 12, 2025. https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html
[i] American Cancer Society. Treating Non-Small Cell Lung Cancer. Accessed November 12, 2025. https://www.cancer.org/cancer/types/lung-cancer/treating-non-small-cell/surgery.html

- Squamous NSCLC: combination of carboplatin with paclitaxel or nabpaclitaxel and pembrolizumab

The following drugs are FDA-approved under accelerated approval for NSCLC with a HER2 mutation:[j]

- Fam-trastuzumab deruxtecan-nxki (Enhertu): indicated for adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy (accelerated approval).
- Zongertinib (Hernexeos) is 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.

Treatment options are limited for patients with previously treated NSCLC harboring HER2 (ERBB2) mutations whose disease has progressed after prior systemic therapy and an unmet medical need exists for more effective therapies.[k]

4. Benefit Assessment

The efficacy of sevabertinib was evaluated in Study SOHO-01 (NCT05099172), an open-label, single-arm, multicenter, multi-cohort clinical study. Eligible subjects (Groups D and E) were required to have previously treated locally advanced or metastatic NSCLC with *HER2 (ERBB2)* tyrosine kinase domain (TKD) activating mutations and have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. *HER2* (*ERBB2*) activating mutations were determined in tumor tissue or plasma by local laboratories prior to enrollment. Subjects with treated, stable and asymptomatic brain metastases were eligible. Subjects with symptomatic CNS metastases, clinically significant cardiac disease, and history of steroid dependent interstitial lung disease (ILD)/pneumonitis were excluded.[l]

- Group D (primary efficacy population): 81 subjects who had received prior systemic therapy but were naïve to therapy targeting *HER2* activating mutations
- Group E (supportive efficacy population): 55 subjects who had received prior systemic therapy and had documented progression to *HER2*-targeted antibody drug conjugates (ADCs)

Due to limited data and insufficient evidence of effectiveness in subjects with non-TKD mutations and squamous histology, FDA considered a revised primary efficacy population to include only subjects with TKD mutations and non-squamous histology.[k] The revised population is Group D (n = 70) plus Group E (N = 52). Subjects received sevabertinib 20 mg orally twice daily until disease progression or unacceptable

[j] U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed November 6, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[k] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.

[l] Bayer Healthcare Pharmaceuticals, Inc. Hyrnuo (sevabertinib). NDA) 219972. Prescribing Information, Final Draft. November 18, 2025.

toxicity. The major efficacy outcomes were confirmed objective response rate (ORR) and duration of response (DOR) as assessed by Blinded Independent Central Review (BICR) using RECIST v1.1.[m,n]

Results showed:[m]

- **Group D - NSCLC Previously Treated, HER2 Targeted Therapy Naïve**: The ORR per BICR was 71% (95% CI: 59, 82) and the median duration of response (DOR) was 9.2 months (95% CI: 6.3, 15), with 54% of responders having an observed DOR ≥ 6 months and 18% of responders with an observed DOR ≥ 12 months.
- **Group E - NSCLC Previously Treated incl. Prior HER2 Targeted Therapy**: The ORR per BICR was 38% (95% CI: 25, 53), with a median DOR of 7.0 months (95% CI: 5.6, NE) and 60% of responders having a DOR ≥ 6 months.

The FDA determined the benefit-risk profile in the indicated population is considered favorable based on the magnitude and durability of the observed responses with sevabertinib, which are consistent with a clinically meaningful advantage over available therapies for the indicated patient population that has a life-threatening disease and an unmet medical need.[m]

The revised indication for approval is the following:[o]

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

5. Risk Assessment & Safe-Use Conditions

The safety of sevabertinib was established in Study SOHO-01. The assessment of safety at the recommended dosage was based on data from subjects with unresectable or metastatic non-squamous NSCLC with HER2 mutations who received sevabertinib 20 mg BID in SOHO-01 (pooled safety population, n = 268). The pooled safety population was used to inform the Warnings and Precautions section of the proposed label.[o] Safety issues identified as significant and serious enough to warrant inclusion in the Warnings and Precautions section of labeling for sevabertinib are diarrhea, hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity.[p] Of those, hepatoxicity and ILD/pneumonitis are severe and life-threatening. Hepatoxicity, ILD/pneumonitis, and ocular toxicity are discussed in the subsections below.

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[m] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.

[n] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[o] Bayer Healthcare Pharmaceuticals, Inc. Hyrnuo (sevabertinib). NDA) 219972. Prescribing Information, Final Draft. November 18, 2025.

[p] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The safety population used to inform the Adverse Reactions section of the proposed label includes subjects with locally advanced or metastatic non-squamous NSCLC with HER2 mutations enrolled in Groups D and E (n = 136). In this safety population, serious adverse reactions occurred in 31% of subjects who received sevabertinib.[q] Serious adverse reactions in ≥ 2% of subjects were diarrhea (6%), pneumonia (3.7%), dyspnea (2.2%), and pleural effusion (2.2%). The FDA's assessment of the fatal adverse events concluded that death occurred in 7% of subjects within 30 days of the last dose of sevabertinib. The majority of the deaths were attributed to disease progression. However, the FDA's assessment could not exclude a potential contribution of sevabertinib to the deaths.[r]

The FDA determined sevabertinib has an acceptable safety profile when assessed in the context of a life-threatening disease. These safety concerns are adequately addressed in the Warnings and Precautions section and dose modification recommendations included in the proposed label.[s]

5.1. Hepatoxicity

Sevabertinib can cause severe hepatotoxicity characterized by elevations of liver function tests (LFTs). In the pooled safety population, hepatotoxicity occurred in 24% of subjects treated with sevabertinib including 3% with Grade 3. Based on laboratory data, 35% of subjects treated with sevabertinib experienced increased alanine aminotransferase (ALT), including 2.3% with Grade 3. Increased aspartate aminotransferase (AST) occurred in 35% of subjects treated with sevabertinib, including 2.3% with Grade 3. Increased bilirubin occurred in 12% of subjects treated with sevabertinib. The median time to first onset of AST or ALT elevation was 1.4 (range 0.2 to 14.5) months.[s]

The safe-use conditions for sevabertinib and associated hepatoxicity includes:[t]

- Monitor liver function tests including ALT, AST, and total bilirubin at baseline prior to administration of sevabertinib, every 2 weeks for the first month, then monthly thereafter as clinically indicated, with more frequent testing in patients who develop transaminase elevations.
- Interrupt, reduce the dose, or permanently discontinue sevabertinib based on the severity of the adverse reaction

Hepatotoxicity	Grade 2, 3 or 4 ALT and/or AST *without* increased total bilirubin or Grade 3 total bilirubin	• Interrupt HYRNUO until recovery to ≤ Grade 1 or baseline. • Resume HYRNUO at the next lower dose.

[q] A Serious Adverse Event (SAE) is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[r] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.

[s] Bayer Healthcare Pharmaceuticals, Inc. Hyrnuo (sevabertinib). NDA) 219972. Prescribing Information, Final Draft. November 18, 2025.

	ALT or AST ≥ 3× ULN with total bilirubin ≥ 2× ULN or Grade 4 total bilirubin	• Permanently discontinue HYRNUO.

Adapted from Table 2:[t] Recommended Hyrnuo Dose Modifications for Adverse Reactions in the Prescribing Information

5.2. Interstitial Lung Disease (ILD)/pneumonitis

ILD/pneumonitis is a known and potentially serious adverse event associated with some TKIs. It often presents with dyspnea, cough, fever, and hypoxemia. The histopathology of ILD induced by TKIs is diffuse alveolar damage (He, 2019). In the pooled safety population, ILD/pneumonitis occurred in two subjects (0.7%) treated with sevabertinib including Grade 3 (0.4%). The median time to first onset of ILD/pneumonitis was 2.6 months (range:1.2 to 4 months).[u]

The safe-use conditions for sevabertinib and associated ILD/pneumonitis include:[u]

- Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever).
- Discontinue sevabertinib upon confirmation of ILD/pneumonitis.

5.3. Ocular toxicity

Sevabertinib can cause ocular toxicity, including corneal epithelial microcysts. In the pooled safety population, ocular toxicity occurred in 14% of subjects treated with sevabertinib, including Grade 1 (11%), Grade 2 (2.6%) and Grade 3 (0.4% [one case of corneal epithelial microcysts with temporary unilateral blindness]).[u]

The safe-use conditions for sevabertinib and associated ocular toxicity include:[u]

- Promptly refer patients presenting with new or worsening eye symptoms to an ophthalmologist.
- Interrupt, reduce the dose or permanently discontinue sevabertinib based on severity

Ocular toxicity	Grade 2	• Interrupt HYRNUO until recovery to Grade ≤1. • Resume HYRNUO at the next lower dose. • Recurrence, permanently discontinue HYRNUO.
	Grade 3 or Grade 4	• Permanently discontinue HYRNUO

Adapted from Table 2:[u] Recommended Hyrnuo Dose Modifications for Adverse Reactions in the Prescribing Information

Ocular toxicity is a known risk of several pharmacologic classes of drugs to treat hematologic and oncologic diseases. They include immune checkpoint inhibitors, fibroblast growth factor receptor inhibitors, human epidermal growth factor 2 inhibitors, MEK inhibitors (mitogen-activated protein kinase inhibitors [trametinib and binimetinib]), BRAF inhibitors (dabrafenib, encorfenib), selective

[t] Bayer Healthcare Pharmaceuticals, Inc. Hyrnuo (sevabertinib). NDA) 219972. Prescribing Information, Final Draft. November 18, 2025.

estrogen receptor modulators, aromatase inhibitors, Breakpoint cluster region–Abelson oncogene inhibitors, Fms-like tyrosine kinase 3 inhibitors, Bruton's tyrosine kinase inhibitors, Anaplastic lymphoma kinase inhibitors, vascular endothelial growth factor receptor inhibitors, Proteasome inhibitors, and antibody-drug conjugates (ADC) (Vitiello, 2024).

The majority of drug-associated ocular toxicity can be managed with observation, topical treatments, and, at most, a reduction in drug dosage (Vitiello, 2024). However, Blenrep (belantamab mafodotin), an ADC, is FDA-approved with a Boxed Warning and REMS with elements to assure safe use (ETASU) to mitigate the risk of ocular toxicity. The incidence and severity of the ocular toxicity associated with belantamab-mafodotin is significantly greater than that of sevabertinib. In Study DREAMM-7, ocular toxicity occurred in 92% of subjects who received belantamab-mafodotin, including Grade 3 or 4 in 77% of subjects compared to 14% of subjects receiving sevabertinib including Grade 3 ocular toxicity in 0.4% in Study SOHO-01.[u]

6. Expected Postmarket Use

Patients with NSCLC including those with a HER2 mutation should have an established relationship with a healthcare provider. The likely prescribers of sevabertinib are oncologists. If approved, sevabertinib will likely be dispensed from outpatient pharmacy settings and primarily be self-administered by the patient at home. Based on the anticipated medication use process, monitoring for diarrhea, hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity should be a collaborative effort between the prescriber and the patient or patient's caregiver. Sevabertinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in labeling.[v]

No concerning care gaps have been identified within the intended scope of practice. Labeling is sufficient to ensure the safe-use conditions for mitigating the risks of sevabertinib in the expected postmarket setting.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of sevabertinib outweigh the risks. Diarrhea, hepatotoxicity, interstitial disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity are the risks listed in the Warnings and Precautions section of the proposed label.

The FDA determined sevabertinib has an acceptable safety profile when assessed in the context of a life-threatening disease. FDA expects the labeling to be sufficient to communicate the risks of sevabertinib. FDA also expects the likely prescribers of sevabertinib (oncologists) to be familiar with managing these risks because other products they prescribe have similar risks.

[u] U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed November 6, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[v] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sevabertinib beyond routine pharmacovigilance and labeling. A post-marketing requirement (PMR) will be issued under the provisions of accelerated approval for verification and further description of the clinical benefit of sevabertinib in the confirmatory trial, Study 22615 (SOHO-02), an open-label, randomized, controlled, global study of sevabertinib versus standard of care pembrolizumab plus platinum-based doublet chemotherapy in patients with previously untreated, locally advanced, or metastatic non-squamous NSCLC harboring HER2 TKD mutations.[w]

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary for sevabertinib to ensure the benefits outweigh the risks. The safety concerns associated with sevabertinib use are well documented. Additionally, healthcare providers who treat NSCLC are likely familiar with the risks of diarrhea, hepatotoxicity, interstitial disease (ILD)/pneumonitis, ocular toxicity, pancreatic enzyme elevation, and embryo-fetal toxicity and the importance of patient monitoring.

Should the Division of Oncology 2 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendix

10.1. References

1. He Y, Zhou C. Tyrosine kinase inhibitors interstitial pneumonitis: diagnosis and management. Translational Lung Cancer Research. 2019:S318-S320.
2. Lilenbaum R. Overview of the initial treatment of advanced non-small cell lung cancer. *UpToDate*. October 13, 2025.
3. Loeffler E, Ancel J, Dalstein V, Deslée G, Polette M, Nawrocki-Raby B. HER2 Alterations in Non-Small Cell Lung Cancer: Biologico-Clinical Consequences and Interest in Therapeutic Strategies. Life (Basel). Dec 29 2023;14(1)doi:10.3390/life14010064
4. Vitiello L, Lixi F, Coco G, Giannaccare G. Ocular Surface Side Effects of Novel Anticancer Drugs. *Cancers (Basel)*. Jan 13 2024;16(2)doi:10.3390/cancers16020344

[w] Food and Drug Administration. Division of Oncology 2. Hyrnuo (sevabertinib). NDA 219972. Multi-disciplinary Review and Evaluation, draft. November 18, 2025.

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