Office of Clinical Pharmacology Review

NDA Number	NDA 213246/S-015
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Submission Date	6/18/2025
Submission Type	Prior Approval Supplement (PAS)
Brand Name	Retevmo® (Selpercatinib)
Dosage Form and Strength	Tablets: 40, 80, 120, and 160 mg Capsules: 40 and 80 mg
Route of Administration	Oral
Approved Indication	• Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test • Adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy • Adult and pediatric patients 2 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory • Adult and pediatric patients 2 years of age and older patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options
Applicant	Eli Lilly and Company
OCP Review Team	Primary Reviewers: Lily Leu (DCPII) Team Leaders: Ye Xiong (DPM), Yixuan Dong (DCPII)
OCP Final Signatory Associate Division Director	Ruby Leong

1. EXECUTIVE SUMMARY

Eli Lilly submitted this Efficacy Supplement with the final results of Study LIBRETTO-121 (J2G-OX-JZJJ) entitled "A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors" to support labeling updates for safety, efficacy, and pharmacokinetics (PK) in pediatric patients with *RET*-altered solid tumors. The clinical pharmacology package for this supplement contains updated PK assessment and population PK (PopPK) analyses which include updated PK data from 10 additional pediatric patients ≥ 6 years of age from the study.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that the proposed labeling updates are acceptable provided the Applicant accepts the recommended changes. This labeling supplement is approvable from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

No new postmarketing requirement (PMR) or postmarketing commitment (PMC) studies are requested by the Office of Clinical Pharmacology.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Regulatory History

RETEVMO® (selpercatinib) is currently approved for treatment of adult patients with locally advanced or metastatic NSCLC with a RET gene fusion and adult and pediatric patients 2 years of age and older with advanced or metastatic MTC, thyroid cancer, and other solid tumors with a RET mutation. The recommendation for accelerated approval in pediatric patients 2 years of age and older was based on the interim efficacy, safety and PK data from Study LIBRETTO-121. Patients received selpercatinib 92 mg/m^2 orally twice daily (BID; maximum 160 mg BID) until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

Given that the exposure in pediatric patients 2 to < 12 years of age following weight-based dosing did not match the adult exposure, body surface area (BSA) tier-based dosages were recommended for this age group (**Table 1**) based on PopPK analysis. The predicted selpercatinib exposures at steady state within each BSA tier in pediatric patients are similar to that in adult patients.

Table 1. BSA tier-based dosage in pediatric patients 2 to <12 years of age

BSA	Recommended dosage
0.33 to 0.65 m^2	40 mg three times daily
0.66 to 1.08 m^2	80 mg twice daily
1.09 to 1.52 m^2	120 mg twice daily
≥1.53 m^2	160 mg twice daily

2.2 Pharmacology and Clinical Pharmacokinetics

Selpercatinib is an oral inhibitor of the RET receptor tyrosine kinase as well as vascular endothelial growth factor receptors 1 and 3 (VEGFR1 and VEGFR3). Refer to the current USPI for detailed pharmacology and PK data of selpercatinib.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The proposed labeling updates to describe the PK of selpercatinib in pediatric patients in Section 8.4 and Section 12.3 are acceptable provided that the Applicant accepts the recommended edits as shown in **Table 2** in Section **3.1**.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

In the current submission, the Applicant proposed to update Section 8.4 and 12.3 in the USPI based on final PK data and updated PopPK analyses. The PK data from additional (n=10) pediatric patients ≥ 6 years of age from Study LIBRETTO-121, along with the existing data in pediatric and adult patients from Studies LIBRETTO-121 and LIBRETTO-001 were incorporated the final PopPK model. The review team confirmed that the model parameter estimates are similar and significant covariates (weight, dose, and Asian race) are the same as the initial PopPK report.

During review of prior Supplement-12 to extend the relevant indications to pediatric patients 2 years of age and older, the Applicant originally proposed (b) (4) PopPK simulations predicted that a dosage of 40 mg three times daily (TID) in patients with low BSA (0.33-0.65 m^2) would have comparable PK to that in adults. As such, Section 8.4 states that the PK comparability between pediatric patients <12 years of age and patients ≥12 years of age and ≥50 kg in weight is based on predicted exposures in pediatric patients. In the current Supplement-15, no additional PK data are generated from the age group (i.e., 2 to 6 years of age) that would fall into the low BSA (0.33-0.65 m^2) group where the recommended dosage of 40 mg TID is based on PopPK simulation.

3.1 Review of Labeling Changes

The proposed labeling updates are generally acceptable provided that the Applicant accepts the recommended changes.

Note that the updated labeling also contains new recommendations for alternative methods of administration via gastrostomy or nasogastric tubes. Given that no PK data are available for the proposed alternative methods of administration, clinical pharmacology defers to CMC to determine the adequacy of this labeling change.

Table 2: Summary of the labeling changes

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