

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218160Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 12, 2023
Application Type and Number:	NDA 218160
Product Name and Strength:	Retevmo (selpercatinib) Tablet, 40 mg, 80 mg, 120 mg, and 160 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Loxo Oncology Inc (Loxo)
PNR ID #:	2023-1044725251
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD
DMEPA 2 Deputy Director:	Chi-Ming (Alice) Tu, PharmD, BCPS

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Retevmo, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. Loxo did not submit an external name study for this proposed proprietary name.

1.1 BACKGROUND

Retevmo (selpercatinib) was originally approved on May 8, 2020 under NDA 213246 and is currently available as 40 mg and 80 mg oral capsules.

Loxo has submitted a non-new molecular entity NDA 218160 for a new oral tablet formulation of Retevmo. Loxo proposed an immediate release, film-coated tablet in strengths of 40 mg, 80 mg, 120 mg, and 160 mg in addition to the existing commercial 40 mg and 80 mg strength capsule formulations. Loxo intends to market selpercatinib tablets under the same proprietary name as the capsule formulation.

Thus, on July 20, 2023, Loxo submitted for our review the name, Retevmo, under NDA 218160 for the newly proposed oral tablet formulation.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on July 20, 2023.

- Intended Pronunciation: reh-TEHV-moh
- Active Ingredient: selpercatinib
- Indication of Use:
 - 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 12 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 12 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 (if radioactive iodine is appropriate).
 - Adult 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.
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 40 mg, 80 mg, 120 mg, and 160 mg

- Dose and Frequency:
 - In adults and pediatric patients 12 years of age or older is based on weight:
 - Less than 50 kg: 120 mg orally twice daily
 - 50 kg or greater: 160 mg orally twice daily

Recommended RETEVMO Dose Reductions for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily

- How Supplied: film-coated tablets in strengths of 40 mg, 80 mg, 120 mg, and 160 mg each in a 60-count, high-density polyethylene bottle.
- Storage: Store at room temperature 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F).

2 METHODS AND DISCUSSION

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Retevmo.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Retevmo would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) concurred with the findings of OPDP's assessment for Retevmo. The Division of Oncology 2 (DO2) concurred with the findings of OPDP's assessment for Retevmo.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Retevmo.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name^a.

2.2.2 Components of the Proposed Proprietary Name

Loxo did not provide a derivation or intended meaning for the proposed proprietary name, Retevmo, in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e., a modifier, route of administration, dosage form, etc.) that can contribute to medication error.

^a USAN stem search conducted on August 15, 2023.

2.2.3 Comments from Other Review Disciplines at Initial Review

On September 6, 2023, the Division of Oncology 2 (DO2) did not forward any comments or concerns relating to Retevmo at the initial phase of the review.

2.2.4 Multiple Dosage Forms Under a Single Proprietary Name

The applicant has proposed to market two dosage forms, capsules and tablets, under the same proprietary name. The proposed tablet formulation in strengths of 40 mg, 80 mg, 120 mg, and 160 mg is intended to offer an improved patient experience by reducing pill burden. In their July 20, 2023 Request for Proprietary Name Review submission, Loxo submitted information on a bioequivalence study that demonstrated bioequivalence between the currently approved commercial capsule formulation and the tablet formulation at the highest strength (1 × 160-mg tablet versus 2 × 80-mg capsules)^b. Additionally, Loxo requested a biowaiver of strengths for 40 mg, 80 mg, and 120 mg tablet formulations.

Table 1 below compares the currently marketed capsule formulation and the proposed tablet formulation.

Table 1. Product Characteristics of Retevmo capsules and Retevmo tablets		
	Retevmo^c	Retevmo (proposed)
Application Number	NDA 213246	NDA 218160
Active Ingredient	selpercatinib	
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 12 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.	

^b Request for Proprietary Name Review for Retevmo (selpercatinib) NDA 218160. July 20, 2023.

<\\CDSESUB1\EVSPROTabletD\nda218160\0006\m1\us\proprietary-names.pdf>

^c Retevmo. DailyMed. National Library of Medicine; October 2023. Available from

<https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=7fa848ba-a59c-4144-9f52-64d090f4d828&type=pdf>

	- Adult and pediatric patients 12 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 (if radioactive iodine is appropriate). - Adult 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.													
Dosage Form	Capsules	Tablets												
Route of Administration	Oral													
Strength	40 mg, 80 mg	40 mg, 80 mg, 120 mg, and 160 mg												
Dose and Frequency	In adults and pediatric patients 12 years of age or older is based on weight : - Less than 50 kg: 120 mg orally twice daily 50 kg or greater: 160 mg orally twice daily Recommended RETEVMO Dose Reductions for Adverse Reactions <table border="1"> <thead> <tr> <th>Dose Reduction</th><th>Patients Weighing Less Than 50 kg</th><th>Patients Weighing 50 kg or Greater</th></tr> </thead> <tbody> <tr> <td>First</td><td>80 mg orally twice daily</td><td>120 mg orally twice daily</td></tr> <tr> <td>Second</td><td>40 mg orally twice daily</td><td>80 mg orally twice daily</td></tr> <tr> <td>Third</td><td>40 mg orally once daily</td><td>40 mg orally twice daily</td></tr> </tbody> </table>		Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater	First	80 mg orally twice daily	120 mg orally twice daily	Second	40 mg orally twice daily	80 mg orally twice daily	Third	40 mg orally once daily	40 mg orally twice daily
Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater												
First	80 mg orally twice daily	120 mg orally twice daily												
Second	40 mg orally twice daily	80 mg orally twice daily												
Third	40 mg orally once daily	40 mg orally twice daily												
How Supplied	40 mg – 60 count bottles 80 mg – 60 and 120 count bottles	All strengths: 60 count bottles												
Storage:	Store at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].													

We note that the proposed dosage forms share the same active ingredient, indication, route of administration, dose and frequency of administration. It is a common and accepted practice to have multiple dosage forms of an active ingredient managed under one proprietary name. Additionally, our routine postmarketing surveillance has not identified any signals attributed to name confusion involving Retevmo. We further acknowledge that, when marketing under the same proprietary name, the differences between the two dosage forms can be communicated and differentiated by labels and labeling.

Therefore, given the aforementioned considerations, we do not object to the Applicant's proposal to market the proposed product with the proprietary name, Retevmo.

2.2.5 *Communication of DMEPA's Determination*

On October 12, 2023, DMEPA 2 communicated our determination to the Division of Oncology 2 (DO2).

3 CONCLUSION

The proposed proprietary name, Retevmo, is conditionally acceptable.

If you have any questions or need clarifications, please contact CAPT Latonia Ford, OSE project manager, at 301-796-4901.

3.1 COMMENTS TO LOXO ONCOLOGY INC

We have completed our review of the proposed proprietary name, Retevmo, and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your submission received on July 20, 2023 are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. **USAN Stems** (<https://www.ama-assn.org/about/united-states-adopted-names-approved-stems>)

USAN Stems List contains all the recognized USAN stems.

2. **Phonetic and Orthographic Computer Analysis (POCA)**

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm

(<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html>).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.^d

^d National Coordinating Council for Medication Error Reporting and Prevention. <https://www.nccmerp.org/about-medication-errors> Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@FDA, Cerner RxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:
- Highly similar pair: combined match percentage score $\geq 70\%$.
 - Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.
 - Low similarity: combined match percentage score $\leq 54\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
 - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names^e. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
 - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

^e Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq 70\%$).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names

may render the names less likely to confusion, provided that the pair does not share a common strength or dose.

<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 55\%$ to $\leq 69\%$).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e., drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) - Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. - Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. - Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names? - Is there different number or placement of cross-stroke or dotted letters present in the names? - Do the infixes of the name appear dissimilar when scripted? - Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) - Do the names have different number of syllables? - Do the names have different syllabic stresses? - Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? - Across a range of dialects, are the names consistently pronounced differently?
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Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 54\%$).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANINE A STEWART
10/12/2023 01:08:16 PM

ASHLEIGH V LOWERY
10/12/2023 01:09:51 PM

CHI-MING TU
10/12/2023 01:48:53 PM