

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213246Orig1s000**

**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)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	213246
<b>PDUFA Goal Date</b>	May 8, 2020
<b>OSE RCM #</b>	2019-2471 and 2473
<b>Reviewer Name(s)</b>	Mei-Yean Chen, Pharm.D.
<b>Team Leader (Acting)</b>	Elizabeth Everhart, MSN, RN, ACNP and Naomi Boston, Pharm.D.
<b>Division Director</b>	Cynthia LaCivita, Pharm.D.
<b>Review Completion Date</b>	April 21, 2020
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Selpercatinib
<b>Trade Name</b>	Retevmo
<b>Name of Applicant</b>	Loxo Oncology, Inc.
<b>Therapeutic Class</b>	A kinase inhibitor
<b>Formulation(s)</b>	40 mg and 80 mg capsules
<b>Dosing Regimen</b>	160 mg orally twice daily

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Retevmo (selpercatinib) is necessary to ensure the benefits outweigh its risks. Loxo Oncology Inc. submitted a New Drug Application (NDA) 213246 for selpercatinib with the proposed indications for the treatment of

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC).
- Adults and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.
- Adults and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who requires systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are proposed for approval under accelerated approval based on overall response rate and duration of response. If approved, the continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

The risks associated with selpercatinib include hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, risk of impaired wound healing, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology 2 (DO2) agree that a REMS is not needed to ensure the benefits of selpercatinib outweigh its risks. There are no FDA approved therapies specifically for RET fusion positive or mutation positive cancers. Metastatic NSCLC, advanced/metastatic MTC, and advanced thyroid cancer are life-threatening conditions with poor survival. The significant overall response rate and durability of these responses to selpercatinib establish the clinical benefit in this population with unmet need. The clinical reviewer believes the risks associated with selpercatinib are manageable with dose reduction, interruption, or discontinuance, and these risks can be adequately handled with the labeling alone.

This reviewer recommends that, if selpercatinib is approved, a REMS is not needed to ensure its benefits outweigh its risks. Hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, risk of impaired wound healing, and embryo-fetal toxicity can be communicated in Section 5 *Warnings and Precautions*, as well as instructions how to withhold, reduce dose, and discontinue therapy in Section 2 *Dosage and Administration*. At the time of this review, none the previously mentioned risks were included in a boxed warning.

# 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)<sup>a</sup> Retevmo (selpercatinib) is necessary to ensure the benefits outweigh its risks. Loxo Oncology Inc. submitted a New Drug Application (NDA) 213246 for selpercatinib with the proposed indication for the treatment of

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC).
- Adults and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.
- Adults and pediatric patients 12 years of age and older with advanced or metastatic RET fusion positive thyroid cancer who requires systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate)

These indications are proposed for approval under accelerated approval based on overall response rate and duration of response. If approved, continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

This application is under review in the Division of Oncology 2 (DO2). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Selpercatinib is a small molecule kinase inhibitor. In enzyme assays, selpercatinib inhibited wild type of RET and multiple mutant RET isoforms, as well as vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR3 at clinically relevant concentrations. RET gene is a known proto-oncogene. Oncogenic activation can occur via mutation or rearrangement.<sup>1</sup> RET alternations have been implicated to be human cancer drivers. In NSCLC, RET rearrangements occur in 1% to 2% of unselected cases. In in vitro and in vivo tumor models, selpercatinib exhibited anti-tumor activity in cells harboring activation of RET protein resulting from gene fusions and mutations.

Selpercatinib is available as 40 mg and 80 mg capsules. The recommended dose is 160 mg taken orally twice daily until disease progression or unacceptable toxicity occurs.<sup>b</sup> Selpercatinib is not currently approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (F): *Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

The following is a summary of the regulatory history for NDA 213246 relevant to this review:

- March 2017: IND 133193 submitted.
- August 2018: Breakthrough therapy designation granted for RET fusion positive NSCLC and for RET mutant MTC
- October 2018: Breakthrough therapy designation granted for RET fusion positive thyroid cancer
- December 2019: NDA 213246 submission received.
- 02/26/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for selpercatinib

### **3 Therapeutic Context and Treatment Options**

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#### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

##### **3.1.1 RET fusion positive Non-small cell lung cancers (NSCLC)**

In the United States (US), it is estimated 228,150 new cases of lung and bronchial cancers and 142,670 deaths due to lung cancer in 2019.<sup>2</sup> NSCLC accounts for 80% of lung cancers and is the most common histological subtype. RET gene fusions have been identified in one to two percent of patients with NSCLC.<sup>c</sup> RET gene fusions are associated with younger age ( $\leq 60$  years of age) and minimal or no prior tobacco exposure. The estimated 5-year survival for patients with clinical stage IIIB NSCLC is about 26%, whereas for patients with stage IV disease, it is about 5%.<sup>c</sup>

##### **3.1.2 RET mutant medullary thyroid cancer (MTC)**

MTC accounts for three to four percent of all thyroid cancers. Twenty-five percent of MTC is associated with familial syndromes (MEN2A, MEN2B and familial MTC). At least 90% of familial cases have an identifiable germline mutation, while approximately 50% of sporadic cases carry a somatic RET mutation. Sporadic MTC usually occurs in the 4<sup>th</sup>-6<sup>th</sup> decades of life, but familial case may occur in very young children. Five-year overall survival (OS) for patients with MTC is 90% and five-year relative survival for patients with stage IV MTC is approximately 39%.<sup>3</sup>

##### **3.1.3 RET fusion-positive thyroid cancer**

In the US, it is estimated 52,890 new cases of thyroid cancer and 2,180 deaths from thyroid cancer in 2020;<sup>2</sup> the 5-year relative survival across subtypes is 98%. Differentiated thyroid carcinoma (DTC) includes the histologic subtypes of papillary, follicular, and Hurthle cell carcinoma. RET rearrangements are identified in 5-10% of papillary thyroid carcinoma and are more common in children than adults.

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<sup>c</sup> 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.*

<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved..*

Localized well-differentiated tumors, such as papillary and follicular thyroid cancer, are typically curable with total thyroidectomy or lobectomy, followed by radioactive iodine therapy for patients at high risk of persistent disease or disease recurrence. Up to 30% of patients may have recurrence. In patients with distant metastases, 5-year survival is 50%, regardless of tumor histology.

Anaplastic thyroid cancer (ATC) accounts for 1.6% of all thyroid cancer and is most lethal among all thyroid cancers due to its aggressive and rapid metastasis. The median life expectancy for patients with ATC is about 4 months and 5-year survival rate is 4%.<sup>4</sup>

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

There are no FDA approved therapies specifically for RET fusion positive or mutation positive cancers. Patients are treated with the approved standard of care for these cancers, irrespective of the presence of a known RET alteration.

#### **3.2.1 RET fusion positive Non-small cell lung cancers (NSCLC)**

For NSCLC, treatment options can include surgery, radiofrequency ablation, radiation, chemotherapy, targeted therapy, and immunotherapy. Platinum based chemotherapy has been the standard of care as the first line chemotherapy, delivering objective response rates (ORRs) of 20-30% and median progression free survival (PFS) of 4-8 months. Other often used chemo drugs include paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed. Targeted therapies may include angiogenesis inhibitors (bevacizumab and ramucirumab), epidermal growth factor receptor (EGFR) inhibitors (erlotinib, afatinib, gefitinib, osimertinib, dacomitinib, osimertinib target cells with the T790M mutation, necitumumab for squamous cell NSCLC), drugs target the abnormal ALK protein (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib), drugs target the abnormal ROS1 protein (crizotinib, ceritinib, lorlatinib, and entrectinib), drugs target cells with BRAF protein and related proteins (dabrafenib and trametinib), and drugs target cells with NTRK gene change (latrectinib and entrectinib). Immunotherapy therapy agents include atezolizumab, pembrolizumab, nivolumab, and durvalumab).<sup>5</sup>

#### **3.2.2 RET mutant medullary thyroid cancer (MTC)**

Vandetanib and cabozantinib, both tyrosine kinase inhibitors, are approved to treat patients with advanced or metastatic, progressive or symptomatic MTC. Neither drug is approved solely for the treatment of patients with RET mutations. The ORRs for vandetanib and cabozantinib in clinical trials to support their approvals were 45% and 28% respectively.

Vandetanib was approved in 2011 with a REMS with Elements To Assure Safe Use (ETASU) given the severity of the risk of QTc prolongation, Torsades de Pointes, and sudden death.<sup>6</sup> Cabozantinib was approved in 2012 to treat patients with progressive, metastatic MTC. The prescribing information does not have a boxed warning, but warnings and precautions only.<sup>7</sup>

#### **3.2.3 RET fusion-positive thyroid cancer**

Most differentiated thyroid cancer (DTC, papillary and follicular thyroid cancers) can be treated effectively with surgery and radioactive iodine therapy. But when these therapies are not effective, targeted drugs may be helpful. Lenvatinib and sorafenib are approved to treat patients with locally

recurrent or metastatic, progressive, radioactive iodine-refractory DTC. The ORR in the clinical trials supporting the approvals of lenvatinib and sorafenib were 65% and 12%, respectively. The prescribing information for lenvatinib<sup>8</sup> and sorafenib<sup>9</sup> do not have a boxed warnings, but warnings and precautions only.

## 4 Benefit Assessment

### 4.1.1 RET fusion positive Non-small cell lung cancers (NSCLC)

The efficacy of selpercatinib in adult patients with advanced RET fusion-positive NSCLC was evaluated in a multicenter, open-label, multiple cohort, clinical trial LIBRETTO-001 (NCT03157128). The trial enrolled patients who had progressed on or were intolerant to available therapies, had no standard or curative therapy available, were unlikely to tolerate or derive significant clinical benefit from standard of care therapy, or had declined standard therapy. The standard of care therapy for NSCLC was defined as platinum-based chemotherapy (or other chemotherapy if not eligible for platinum) or Programmed Death (PD)-1/PD-L1 immunotherapy, or both. Identification of a RET gene was determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). Patients received selpercatinib 160 mg orally twice daily until unacceptable toxicity or disease progression.

The major efficacy outcome measures were confirmed ORR and duration of response (DOR) as determined by a blinded independent review committee (BIRC) according to response evaluation criteria in solid tumors (RECIST) v1.1.

#### Metastatic RET fusion-positive NSCLC previously treated with platinum chemotherapy

The efficacy for patients with RET fusion-positive NSCLC previously treated with platinum chemotherapy was evaluated on 105 adult patients enrolled into LIBRETTO-001. The median age was 61 years (range 23-81), 59% of patients were female, 52% were White, 38% were Asian, 4.8% were Black, and 3.8% were Hispanic/Latino. RET gene fusions were detected in patients using NGS in 90% of patients, 9% using FISH, and 2% using PCR. All patients received prior systemic therapy; 55% had prior anti-PD-1/PD-L1 therapy. Table 1 is the summary of efficacy result.

**Table 1** Efficacy results in the LIBRETTO-001 (b) (4) metastatic RET fusion-positive NSCLC previously treated with platinum chemotherapy<sup>10</sup>

	Selpercatinib, n=105
Overall response rate (95% confidence interval)	64% (54%, 73%)
Complete response	1.9%
Partial response	62%

Duration of response (months)	
Median (95% confidence interval)	17.5 (12.0, Not estimable)
% with ≥ 6 months	81%

An exploratory subgroup analysis of the 58 patients who received an anti-PD-1 or anti-PD-L1 therapy, the ORR was 66% (95% CI:51.9, 77.5) and the median DOR was 12.5 months (95% CI: 8.3, not estimable). In the exploratory subgroup analysis of 11 patients with measurable CNS lesions, the ORR was 91% (95%CI 58.7, 99.8) and 70% of these patients had a DOR of ≥ 6 months.

Treatment-naïve metastatic RET fusion-positive NSCLS

The efficacy for patients with treatment-naïve RET fusion-positive NSCLC was evaluated in 39 adult patients enrolled into LIBRETTO-001. The median age was 61 years (range 23-86), 56% of patients were female, 72% were White, 18% were Asian, and 8% were Black. RET gene fusions were detected in patients using NGS in 92% of patients and 8% using FISH. Table 2 is the summary of efficacy result.<sup>d</sup>

**Table 2** Efficacy results in the LIBRETTO-001 (b) (4) treatment-naïve metastatic RET fusion-positive NSCLC.<sup>10</sup>

	Selpercatinib, n=39
Overall response rate (95% confidence interval)	(b) (4) (70%, 94%)
Complete response	0%
Partial response	(b) (4) %
Duration of response (months)	
Median (95% confidence interval)	Not estimable (12, Not estimable)
% with ≥ 6 months	58%

**4.1.2 RET mutant medullary thyroid cancer (MTC)**

The efficacy of selpercatinib in adult patients and pediatric patients ≥ 12 years old with RET mutant MTC was evaluated in a multicenter, open-label, multiple cohort, clinical trial LIBRETTO-001 (NCT03157128).

<sup>d</sup> 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.*

The trial enrolled patients who had progressed on or were intolerant to available therapies, had no standard or curative therapy available, were unlikely to tolerate or derive significant clinical benefit from standard of care therapy, or had declined standard therapy. The standard of care for MTC was defined as vandetanib or cabozantinib or both agents.

RET mutant MTC previously treated with cabozantinib or vandetanib

The efficacy of selpercatinib in patients with RET mutant advanced MTC was evaluated on 55 patients previously treated with cabozantinib or vandetanib enrolled into LIBRETTO-001. The median age was 57 years (range 17 to 84) with one pediatric patient, 66% of patients were male, 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. All patients received prior systemic therapy. RET mutation status was detected in 82% of patients using NGS and 16% using PCR. Table 3 is the summary of efficacy result.

**Table 3** Efficacy results in the LIBRETTO-001 (b) (4) RET mutant MTC previously treated with cabozantinib or vandetanib<sup>10</sup>

	Selpercatinib, n=55
Overall response rate (95% confidence interval)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of response (months)	
Median (95% confidence interval)	Not estimable (19.1, Not estimable)
% with ≥ 6 months	76%

Cabozantinib or vandetanib naïve RET mutant MTC

The efficacy of selpercatinib in patients with RET mutant MTC was evaluated on 44 patients who were not treated with cabozantinib or vandetanib enrolled into LIBRETTO-001. The median age was 58 years (range 15 to 82) with two patient aged 12 to 16 years, 69% of patients were male, 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. All patients had metastatic disease, 18% had received one or two prior systemic therapies. RET mutation status was detected in 78% of patients using NGS and 18% using PCR. Table 4 is the summary of efficacy result.

**Table 4** Efficacy results in the LIBRETTO-001 (b) (4) RET mutant MTC (b) (4)<sup>10</sup>

	Selpercatinib, n=88
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Overall response rate (95% confidence interval)	73% (62%, 82%)
Complete response	11%
Partial response	61%
Duration of response (months)	
Median (95% confidence interval)	22.0 (Not estimable, Not estimable)
% with ≥ 6 months	61%

### 4.1.3 **RET fusion-positive thyroid cancer**

The efficacy of selpercatinib was evaluated in 19 adult patients with advanced RET fusion positive thyroid cancer enrolled in a multicenter, open-label, multiple cohort, clinical trial (LIBRETTO-001, NCT 03157128). The trial enrolled patients who had progressed on or or were intolerant to available therapies, had no standard or curative therapy available, were unlikely to tolerate or derive significant clinical benefit from standard of care therapy, or had declined standard therapy. The standard of care for RET fusion positive thyroid cancer was defined as radioactive iodine (as appropriate) followed by sorafenib or lenvatinib for patients with differentiated thyroid cancer. The median age was 54 years (range 20 to 88), 52% of patients were male, 74% were White, 5% were Hispanic/Latino, 10.5% were Asian, and 5.3% were Black. All patients received prior systemic therapy. RET mutation status was detected in 93% of patients using NGS tumor samples, and in 7% using blood samples. Table 5 is the summary of efficacy result.

**Table 5** Efficacy results in the LIBRETTO-001 (b) (4) RET fusion positive thyroid cancer<sup>10</sup>

	Selpercatinib, previously treated, n=19	Selpercatinib, systemic therapy naïve, n=8
Overall response rate (95% CI)	79 % (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	(b) (4)%
Partial response	74 %	(b) (4)%
Duration of response (months)		
Median (95% CI)	18.4 (7.6, NE)	NE (NE,NE)
% with ≥ 6 months	(b) (4)%	75%

## 5 Risk Assessment & Safe-Use Conditions

The safety of selpercatinib was evaluated in 702 patients in the LIBRETTO-001 Study. Selpercatinib was administered 160 mg orally twice daily as a single agent in 95% of patients. The serious risks<sup>e</sup> associated with selpercatinib are discussed below.

### 5.1 QT INTERVAL PROLONGATION

QT interval prolongation was observed in patients received selpercatinib during the clinical trial. Among 697 patients who had baseline and post treatment assessments, 6% of patients had QTcF interval to >500 msec and 15% of patients increased by at least 60 msec over baseline.<sup>12</sup> There were no reports of Torsades de Pointes (TdP) and sudden death.

A thorough QT (TQT) study in healthy subjects was used to evaluate the effect of selpercatinib on the QTc interval. At the proposed dosing regimen (160 mg twice daily), the mean increase in QTc is 10.6 msec. Concentration-dependent QTc prolongation was detected in the TQT study. Interdisciplinary Review Team for Cardiac Safety Studies of QT consultatin review states in section 3.2.5 Cardiac Safety Analysis : *“There were no deaths, serious adverse events, or subject discontinuations due to adverse events (AEs)”*.<sup>11</sup>

If approved, the prescribing information will advise the healthcare providers (HCPs) (b) (4)  
(b) (4)  
(b) (4). Labeling recommends (b) (4)  
(b) (4)  
(b) (4). Labeling will recommend (b) (4) TSH be  
obtained at baseline (b) (4) ECGs (b) (4) more frequently in patients who  
require treatment with concomitant drugs known to prolong QT interval.<sup>10</sup>

### 5.2 HEPATOTOXICITY

(b) (4) serious hepatic adverse reactions occurred in 2 (b) (4)% of patients treated with selpercatinib. (b) (4)  
(b) (4)  
(b) (4).<sup>10</sup> Among the 692 patients who received selpercatinib and had a baseline and post therapy laboratory result, 51% of patients had increased AST of any grade, including grade 3-4 in 8%; 45% of patients had increased ALT of any grade, including grade 3-4 in 9%. The median time to first onset for AST increase was 4.1 weeks (range: 5 days to 2 years) and ALT increase was 4.1 weeks (range: 6 days to 1.5 years).

The labeling will advise HCPs to monitor ALT and AST prior to initiating selpercatinib, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Section Dosage

<sup>e</sup> 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.*

Modifications for Adverse Reactions will have instructions how to withhold and modify the selpercatinib dosage.

### **5.3 HEMORRHAGIC EVENTS**

In the selpercatinib clinical trial, serious hemorrhagic events, including fatal events, were reported. Among 702 patients treated with selpercatinib, a hemorrhagic event occurred in 15% of patients, including grade  $\geq 3$  occurred in 2.3% of patients. Three patients (0.8%) died of hemorrhagic event, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

HCPs will be advised in the labeling to permanently discontinue selpercatinib in patients with severe or life-threatening hemorrhage.

### **5.4 HYPERTENSION**

Thirty-five percent of patients was reported to have hypertension, including 17% of patients with grade 3. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced. Treatment-emergent hypertension was managed with anti-hypertensive drugs.

The labeling will advise HCPs not to initiate selpercatinib in patients with uncontrolled hypertension. Monitor blood pressure after one week of therapy and then monthly and as clinically indicated. In the labeling, Section 2.7 Dosage Modifications for Adverse Reactions will have instructions how to withhold and modify the selpercatinib dosage for hypertension.

### **5.5 HYPERSENSITIVITY**

Hypersensitivity occurred in 4.3% of patients received selpercatinib, including 1.6% with a grade 3 event. The median time to onset was 1.7 weeks (range: 6 days to 1.4 years). Fever, rash and arthragias or myalgias were typical signs and symptoms of hypersensitivity reactions.

HCPs will be advised to withhold selpercatinib and begin corticosteroids at a dose of 1 mg/kg if hypersensitivity occurs. Permanently discontinue selpercatinib for recurrent hypersensitivity.

### **5.6 RISK OF IMPAIRED WOUND HEALING**

Impaired wound healing can occur in patients who receive drugs that inhibit VEGF signaling pathway. Therefore, selpercatinib has the potential to impair wound healing.

The labeling will advise HCPs to withhold selpercatinib for at least (b) (4) days prior to elective surgery and not to administer for at least 2 weeks following major surgery and until adequate wound healing.

### **5.7 EMBRYO-FETAL TOXICITY**

Selpercatinib can cause fetal harm, based on data from animal reproduction studies, when administered to a pregnant woman. The labeling will advise HCPs to educate pregnant women of the potential risk to a fetus and to use effective contraception during (b) (4) and for at least one week (b) (4)

## **6 Expected Post-market Use**

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If approved, it is expected that oncologists will be the likely health care providers to prescribe selpercatinib in both inpatient and outpatient settings.

## 7 Risk Management Activities Proposed by the Applicant

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The Applicant did not propose any risk management activities for selpercatinib beyond routine pharmacovigilance and labeling.

## 8 Discussion of Need for a REMS

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The Clinical Reviewer recommends approval of selpercatinib on the basis of the efficacy and safety information currently available.<sup>12</sup>

There are no FDA approved therapies specifically for RET fusion positive or mutation positive cancers including RET fusion-positive NSCLC, RET-mutant MTC, and RET fusion-positive non-medullary thyroid cancers. All these cancers are life-threatening with poor survival. The clinical reviewer concluded that the significant ORR and durability of these responses to selpercatinib establish the clinical benefit in this population with unmet need.<sup>13</sup> The clinical reviewer believes the risks associated with selpercatinib are manageable with dose reduction, interruption, or discontinuance, and that these risks can be adequately handled with the labeling alone.

This reviewer recommends that, if selpercatinib is approved, a REMS is not necessary to ensure its benefits outweigh its risks. Hepatotoxicity, hypertension, QT prolongation, hemorrhagic events, hypersensitivity, risk of impaired wound healing, and embryo-fetal toxicity will be communicated in Section 5 *Warnings and Precautions*, as well as instructions how to withhold, reduce dose, and discontinue therapy in Section 2 *Dosage and Administration*. At the time of this review, none of these risks were included in a boxed warning.

## 9 Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable; therefore, a REMS is not necessary for selpercatinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>1</sup> Gautschi O, Milia J, et al Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry J Clin Oncol. 2017 May 1; 35(13): 1403-1410

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- <sup>2</sup> Surveillance, Epidemiology, and End Results (SEER) program, [www.seer.cancer.gov](http://www.seer.cancer.gov), accessed 03/09/2020
- <sup>3</sup> 5-year relative survival rates for thyroid cancer [www.cancer.org/cancer/thyroid-cancer/detection-diagnosis-staging/survival-rates.html](http://www.cancer.org/cancer/thyroid-cancer/detection-diagnosis-staging/survival-rates.html), accessed 03/09/2020
- <sup>4</sup> Thyroid cancer : statistics [www.cancer.net/cancer-types/thyroid-cancer/statistics](http://www.cancer.net/cancer-types/thyroid-cancer/statistics), accessed 03/09/2020
- <sup>5</sup> Treating non-small cell lung cancer, [www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html](http://www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html), accessed 03/24/2020
- <sup>6</sup> Caprelsa (vandetanib) [www.REMS@FDA](http://www.REMS@FDA), accessed 03/24/2020
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- <sup>8</sup> Lenvima (lenvatinib) [www.Drugs@FDA](http://www.Drugs@FDA), accessed 03/24/2020
- <sup>9</sup> Nexavar (sorafenib) [www.Drugs@FDA](http://www.Drugs@FDA), accessed 03/24/2020
- <sup>10</sup> Selpercatinib draft prescribing information, 04/20/2020
- <sup>11</sup> Zheng N, Garnett C et al Selpercatinib NDA 213246 QT Consultation Reviw, Interdisciplinary Review Team for Cardiac Safety Studies DARRTS ID# 4570225
- <sup>12</sup> Bradford D. Selpercatinib NDA 213246 midcycle presentation, 02/12/2020
- <sup>13</sup> Selpercatinib NDA 213246 Multi-disciplinary review, accessed 0320/2020

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/s/  
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