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<th>Application Type</th>
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<tr>
<td>Application Number</td>
<td>213973</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>June 12, 2020</td>
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<tr>
<td>OSE RCM #</td>
<td>2019-2212 and 2214</td>
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| Reviewer Name(s)  | Mei-Yean Chen, Pharm.D.    |
| Team Leader (Acting) | Elizabeth Everhart, MSN, RN, ACNP |
| Division Director | Cynthia LaCivita, Pharm.D. |
| Review Completion Date | April 22, 2020            |
| Subject            | Evaluation of Need for a REMS |

| Established Name | Ripretinib              |
| Trade Name       | Qinlock                 |
| Name of Applicant | Deciphera Pharmaceuticals Inc. |
| Therapeutic Class | A kinase inhibitor      |
| Formulation(s)   | 50 mg Tablet            |
| Dosing Regimen   | 150 mg orally once daily |
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Qinlock (ripretinib) is necessary to ensure the benefits outweigh its risks. Deciphera Pharmaceuticals Inc. (Deciphera) submitted a New Drug Application (NDA) 213973 for ripretinib with the proposed indication for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. The risks associated with ripretinib include dermatologic toxicities, new primary cutaneous malignancies, hypertension, cardiac dysfunction, impaired wound healing, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and the Division of Oncology 3 (DO3) agree that a REMS is not needed to ensure the benefits of ripretinib outweigh its risks. Ripretinib is proposed to treat patients with advanced GIST who have received prior therapies with imatinib, sunitinib, and regorafenib. This patient population with a serious and life-threatening, rare cancer, has a high unmet medical need. Patients randomized to the ripretinib arm in the INVICTUS trial demonstrated a significant and clinically meaningful improvement in progression free survival compared to the placebo arm with a tolerable safety profile.

This reviewer recommends that, if ripretinib is approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks associated with ripretinib: dermatologic toxicities, new primary cutaneous malignancies, hypertension, cardiac dysfunction, impaired wound healing, and embryo-fetal toxicity will be communicated in Section 5 Warnings and Precautions; labeling will also include instructions on how to withhold, reduce dose, and discontinue therapy in Section 2 Dosage and Administration. At the time of this review, none of these risks will have a boxed warning. Practitioners, typically oncologists, who will prescribing ripretinib should be familiar by their experience and training in the management of these toxicities.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)a Qinlock (ripretinib) is necessary to ensure the benefits outweigh its risks. Deciphera submitted a New Drug Application (NDA) 213973 for ripretinib with the proposed indication for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

a Section 505 1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
Ripretinib is a tyrosine kinase inhibitor that inhibits KIT and platelet-derived growth factor receptor alpha (PDGFRα) kinase signaling. By binding to both the switch pocket and the activation loop to inactivate the kinase, ripretinib prevents downstream signaling and cell proliferation in wild type and primary and secondary mutations. Approximately 80% of GISTs have a mutation in KIT and approximately 10% have a mutation in PDGFRα. These mutations act to disrupt the autoinhibited forms of KIT and PDGFRα kinases and cause constitutive activation of downstream signaling, leading to uncontrolled cell growth and cell transformation, resulting tumor growth and metastasis.

Ripretinib is available as a 50 mg tablet. The recommended dose is 150 mg taken orally once daily until disease progression or unacceptable toxicity occurs. Ripretinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 213973 relevant to this review:

- 10/02/2014: Orphan drug designation granted.
- 06/21/2019: Fast track designation granted.
- 10/09/2019: pre-NDA for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.
- 10/10/2019: Breakthrough therapy designation granted.
- 12/23/2019: NDA 213973 submission received.
- 03/12/2020: 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 ripretinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Gastrointestinal stromal tumors (GISTs) account for about one percent of primary Gastrointestinal (GI) tumors, but they are the most common mesenchymal neoplasms of the GI tract. GISTs are usually found in the stomach or small intestine. The tumors are thought to grow from specialized cells found in the GI tract called interstitial cells of Cajal (ICC) or precursors to these cells. In the United States (US), there are approximately 5,000 new cases of GIST diagnosed each year. GISTs occur predominantly in middle-aged and older people, usually between ages 40 and 70 and rarely in those under the age of 40.

\(^{b}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

\(^{c}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
Prior to 1998, GISTs were considered to be derived from smooth muscle. By the early 1990s, it became apparent that GISTs represent a distinct entity from other mesenchymal tumors of the GI tract, such as leiomyomas and leiomyosarcomas. In GISTs, there is near-universal expression of the CD 117 antigen, while leiomyosarcomas, leiomyomas, and other spindle cell tumors of GI tract are typically CD 117 negative. CD 117 antigen is synonymous with the transmembrane KIT receptor tyrosine kinase. GISTs can carry a mutation in the KIT gene, leading to a structural variant of the KIT protein, which is abnormally activated and enables oncogenic signaling in the cell. More than 80% of GISTs carry a mutation in the KIT gene. The majority of GISTs appears to be sporadic, about five percent of patients have one of several familial autosomal dominant syndromes, including primary familial GIST syndrome, neurofibromatosis type 1 (NF1), and Carne-Stratakis syndrome. The clinical presentations of GISTs are highly variable; the main prognostic determination are tumor size, mitotic rate, and tumor location. With long follow-up, it became clear that virtually all GISTs have the potential for malignant behavior. Since all GISTs are regarded as potentially malignant, consensus classifications focus on stratifying lesions according to the relative risk of recurrence and metastasis.

Some GISTs are asymptomatic and are discovered incidentally during an endoscopic exam or on cross-sectional imaging done for another purpose. The clinical presentations may include GI bleed (28% in small intestine & 50% in stomach), abdominal pain/discomfort (8-17%), acute abdomen (2-14%), and asymptomatic abdominal mass (5%). GISTs metastasize to the liver and peritoneum frequently, and rarely to regional lymph nodes. They uncommonly metastasize to the lungs.

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There was no known effective treatment for unresectable or metastatic GISTs prior to the year 2000. It has long been known that GI tract sarcomas have lower response rates to chemotherapy than other sites of soft tissue sarcoma. After the finding of mutational activation of KIT or PDGFRα stimulate growth of GISTs cancer cells, therapy of GISTs was fundamentally changed. This led to effective systemic treatments in the form of small molecule TKIs. Imatinib (Gleevec) was approved in 2003 for two indications:

- to treat patients with chronic myeloid leukemia (CML)
- to treat patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST.

Imatinib has become first-line therapy for metastatic or inoperable GIST since then. Unfortunately, most patients with GIST develop resistance to imatinib due to the emergence of secondary KIT mutations.

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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.
Table 1 below summarizes the current FDA approved TKIs to treat GISTs.

<table>
<thead>
<tr>
<th>Trade Name (Generic)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Warnings &amp; Precautions</th>
<th>Boxed Warning (BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleevec (imatinib)</td>
<td>Kit (CD117)+ unresectable and/or metastatic</td>
<td>400 mg oral daily</td>
<td>Edema, cytopenia, left ventricular dysfunction, hepatotoxicity, hemorrhage, GI disorder, hypereosinophilic cardiac toxicity, dermatologic toxicities, hypothyroidism, &amp; renal toxicity</td>
<td>No BW</td>
</tr>
<tr>
<td>Sutent (sunitinib)</td>
<td>After GIST progression on or intolerance to imatinib</td>
<td>50 mg oral daily, 4 weeks on &amp; 2 weeks off</td>
<td>hepatotoxicity, cardiovascular events, QT prolongation, hypertension, bleeding, tumor lysis syndrome, thrombotic microangiopathy, proteinuria, dermatologic toxicities, thyroid dysfunction, osteonecrosis of the jaw, wound healing</td>
<td>BW for hepatotoxicity</td>
</tr>
<tr>
<td>Stivarga (regorafenib)</td>
<td>Locally advanced, unresectable or met. GIST previously treated with imatinib and sunitinib</td>
<td>160 mg oral daily, 21 days on &amp; 7 days off</td>
<td>Hepatotoxicity, hemorrhage, dermatological toxicity, hypertension, cardiac ischemia, reversible posterior leukoencephalopathy syndrome, GI perforation, impair wound healing</td>
<td>BW for hepatotoxicity</td>
</tr>
<tr>
<td>Ayvakit (avapritinib)</td>
<td>GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutation</td>
<td>300 mg oral once daily</td>
<td>Intracranial hemorrhage, Central nervous system effects, and embryo-fetal toxicity</td>
<td>No BW</td>
</tr>
</tbody>
</table>

4 Benefit Assessment

The INVICTUS (NCT03353753) trial, an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial, was used to evaluate the efficacy of ripretinib. This trial enrolled patients with unresectable, locally advanced or metastatic GIST who were required to have received prior therapy with imatinib, sunitinib, and regorafenib. Ripretinib 150 mg or placebo orally once daily was
administered to patients until disease progression or unacceptable toxicity. Tumor responses were assessed every 28 days through the first four months and then every 56 days thereafter. Patients randomized to the placebo arm could be treated with ripretinib at the time of disease progression.

Progression free survival (PFS) was the major efficacy endpoint. A progressively growing new tumor nodule within a pre-existing tumor mass must have met specific criteria to be considered unequivocal evidence of progression. Additional efficacy measures included objective response rate (ORR) by blinded independent central review (BICR) and overall survival (OS). The median age of study population was 60 years (range: 29 to 83 years), with 39% aged ≥ 65 years; 57% male; 75% White; and 92% Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Sixty-three percent of patients received 3 prior therapies and 37% received 4 or more therapies. Among patients randomized to placebo, 66% switched to ripretinib after disease progression. Table 2 summarizes efficacy results from INVICTUS trial.

Table 2 Efficacy results of INVICTUS

<table>
<thead>
<tr>
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<th>Ripretinib, N=85</th>
<th>Placebo, N=44</th>
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<tbody>
<tr>
<td><strong>Median PFS (months) (95% CI)</strong></td>
<td>6.3 (4.6, 6.9)</td>
<td>1.0 (0.9, 1.7)</td>
</tr>
<tr>
<td>p-value &lt; 0.0001</td>
<td></td>
<td></td>
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<tr>
<td><em><em>ORR (%) (95% CI</em>)</em>*</td>
<td>9 (4.2, 18)</td>
<td>0 (0.8)</td>
</tr>
<tr>
<td>p-value 0.0504</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of Deaths, N (%)</strong></td>
<td>26 (31%)</td>
<td>26 (59%)</td>
</tr>
<tr>
<td>*<em>Median OS (months) (95% CI</em>)**</td>
<td>15 (12, 15)</td>
<td>7 (4.1, 12)</td>
</tr>
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* CI: confidence interval

The median of PFS was 6.3 months in the ripretinib arm versus 1 month in the placebo arm. The medical officers concluded that the results demonstrated a statistically significant and clinical meaningful improvement PFS for ripretinib compared to placebo.

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*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.

Reference ID: 4596047
5 Risk Assessment & Safe-Use Conditions

The safety of ripretinib was evaluated in the pooled safety population that included 351 patients with advanced solid tumors in trials who received any dose of ripretinib. All risks associated with ripretinib listed below reflect exposure to ripretinib as a single agent and are currently included in the draft labeling in Warnings and Precautions. There were 26 deaths (31%, N=85) reported in ripretinib arm versus 26 deaths (59%, N=44) in the placebo arm.

5.1 Dermatologic Toxicities

Bullous and Exfoliative Skin Disorders

In the pooled safety population, 0.6% of 351 patients were reported to have developed bullous and exfoliative skin disorders, including cases of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis.

If approved, healthcare providers (HCPs) will be advised to permanently discontinue ripretinib if patients develop severe bullous, blistering, or exfoliating conditions.

Hand-Foot Skin Reactions

In the INVICTUS trial, grade 1-2 hand-foot skin reaction was reported in 21% of 85 patients who received ripretinib. Based on severity of the hand-foot skin reaction, HCPs will be advised to withhold, and then resume at same or reduced, or permanently discontinue ripretinib according the instructions in Dosage and Administration.

5.2 New Primary Cutaneous Malignancies

Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma was reported in 4.7% of 85 patients who received ripretinib in INVICTUS trial. The median time to event was 4.6 months (range: 3.8 to 6 months). In the pooled safety population, cutaneous squamous cell carcinoma occurred in 9% of 351 patients.

Melanoma

Melanoma was observed in 2.4% of 85 patients who received ripretinib in INVICTUS trial. In the pooled safety population, melanoma occurred in 1% of 351 patients.

If approved, HCPs will be advised to perform dermatologic evaluation prior to initiation of ripretinib and routinely during therapy.

5.3 Hypertension

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.
Grade 1-3 hypertension was reported in 14% of patients who received ripretinib in the INVICTUS trial. Grade 3 hypertension was observed in 7% of treated patients. Based on reported vital signs, Grade 3 hypertension was observed in 13% of patients who received ripretinib in INVICTUS trial, while 45% had at least a one grade increase in blood pressure from baseline.

The labeling will advise HCPs to optimize blood pressure prior to initiating ripretinib and to initiate or adjust antihypertensive medications accordingly. Dosage and Administration in the labeling will instruct how to withhold, and then resume at the same or reduced dose, or discontinue the drug.

5.4 CARDIAC DYSFUNCTION
Cardiac dysfunction, including cardiac failure, was reported in 1% of the 85 patients who received ripretinib in INVICTUS trial. In the pooled safety populations, 3.4% of 351 patients was observed to have cardiac dysfunction. Cardiomyopathy, defined as decrease in left ventricular ejection fraction (LVEF) below 50% with an absolute decrease in LVEF $\geq$ 10% below baseline as detected by echocardiography, occurred in 2.3% of the patients who received ripretinib in INVICTUS trial. All of these patients had Grade 3 ejection fraction decrease. In the pooled safety population, 3.4% of patients had evidence of cardiomyopathy as measured by echocardiography. All of these patients had Grade 3 ejection fraction decreases.

HCPs will be advised to assess ejection fraction by echocardiogram or multigated acquisition (MUGA) scan prior to initiating ripretinib and to monitor patients with cardiovascular risk factors more frequently.

5.5 IMPAIRED WOUND HEALING
Vascular endothelial growth factor (VEGF) inhibitor can impair wound healing. Ripretinib has the potential to affect wound healing adversely.

The labeling will advise HCPs to withhold ripretinib for at least one week prior to elective surgery. For major surgical procedures, hold ripretinib for at least two weeks and until adequate wound healing.

5.6 EMBRYO-FETAL TOXICITY
Ripretinib can cause fetal harm when administered to a pregnant woman, based on findings from animal studies and its mechanism of action.

The labeling will advise HCPs to educate pregnant women of the potential risk to a fetus, instructing females of reproductive potential to use effective contraception during ripretinib therapy and for one week after the final dose. Males with female partners of reproductive potential are instructed to use effective contraception during ripretinib therapy and for at least one week after the last dose.

6 Expected Post market Use
If approved, it is expected that oncologists will be the likely health care providers to prescribe ripretinib in both inpatient and outpatient settings.
7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ripretinib on the basis of the efficacy and safety information currently available. GISTs are the most common nonepithelial neoplasms affecting the Gastrointestinal tract. Patients with metastatic GIST have only a 52% 5-year survival. Ripretinib is proposed to treat patients with advanced GIST who have received prior therapies with imatinib, sunitinib, and regorafenib. This patient population with a serious and life-threatening, rare cancer, has a high unmet medical need. Patients randomized to the ripretinib arm in the INVICTUS trial demonstrated a significant and clinically meaningful improvement in PFS compared to the placebo arm with a tolerable safety profile.9

This reviewer recommends that, if ripretinib is approved, a REMS is not needed to ensure its benefits outweigh its risks. Dermatologic toxicities, new primary cutaneous malignancies, hypertension, cardiac dysfunction, impaired wound healing, and embryo-fetal toxicity will be communicated in Section 5 Warnings and Precautions; labeling will also include instructions on how to withhold, reduce dose, and discontinue therapy in Section 2 Dosage and Administration. At the time of this review, none of these risks warrants a boxed warning. Practitioners, typically oncologists, who will prescribing ripretinib should be familiar by their experience and training in the management of these toxicities.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for ripretinib 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

10.1 REFERENCES


4 Imatinib (Gleevec) prescribing information, www.Drugs@FDA, accessed 03/05/2020

5 Sunitinib (Sutent) prescribing information, www.labeling.pfizer.com, accessed 04/08/2020

6 Regorafenib (Stivarga) prescribing information. www.Drugs@FDA, accessed 03/05/2020

7 Avapritinib (Ayvakit) prescribing information. www.Drugs@FDA, accessed 04/08/2020

8 Ripretinib draft prescribing information on 04/07/2020

9 Multi-disciplinary review of ripretinib NDA 213973, accessed 04/03/2020
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/

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04/22/2020 08:52:26 AM

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Reference ID: 4596047