RXADVANCE
2 Park Central Drive
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NEW DRUG APPROVAL

Brand Name	Qinlock™
Generic Name	ripretinib
Drug Manufacturer	Deciphera Pharmaceuticals, LLC

New Drug Approval

FDA Approval Date: May 15, 2020

The FDA granted this application Priority Review and Fast Track designation, as well as Breakthrough Therapy designation, which expedites the development and review of drugs that are intended to treat a serious condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies. Qinlock also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases. This review used the Real-Time Oncology Review, which streamlined data submission prior to the filing of the entire clinical application, and the Assessment Aid, a voluntary submission from the applicant to facilitate the FDA's assessment.

Qinlock may cause harm to a developing fetus or a newborn baby. Health care professionals should advise pregnant women of this risk and should advise both females of reproductive potential and male patients with female partners of reproductive potential, to use effective contraception during treatment and for one week after the last dose. Patients should be advised not to breastfeed while taking Qinlock.

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Gastrointestinal stromal tumor (GIST) is a type of tumor that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant. Learn about gastrointestinal stromal tumor and find information on how we support and care for people with GIST before, during, and after treatment.
Gastrointestinal stromal tumor is a disease in which abnormal cells form in the tissues of the gastrointestinal tract.
Genetic factors can increase the risk of having a gastrointestinal stromal tumor.
Signs of gastrointestinal stromal tumors include blood in the stool or vomit.
Tests that examine the GI tract are used to diagnose gastrointestinal stromal tumors.
Very small GISTs are common.
Certain factors affect prognosis (chance of recovery) and treatment options.

Although they comprise fewer than 1% of all gastrointestinal (GI) tumors, GIST are the most common mesenchymal tumors of the GI tract. It has been estimated that there are 3,300 to 6,000 new GIST cases per year in the United States. A study based on Surveillance, Epidemiology and End Results (SEER) registry data found that the age-adjusted yearly incidence of GIST in the United States was 6.8 per million from 1992 to 2000. However, the true incidence is not known, in part because many tumors have not been tested for the characteristic KIT or platelet-derived growth factor receptor alpha (PDGFRA) gene mutations. In addition, small, indolent GIST, only a few millimeters in diameter, are common in the general population and are not included in cancer registries. GIST are equally distributed across all geographic and ethnic groups and men and women are equally affected. Most patients present between the ages of 50 and 80. The vast majority of GIST are sporadic, but there are rare familial forms associated with the characteristic heritable mutations in the KIT gene (or, rarely, in succinate dehydrogenase genes in Carney-Stratakis syndrome). Familial GIST may present as multiple primary tumors.

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Efficacy

Qinlock's approval was based on the results of an international, multi-center, randomized, double-blind, placebo-controlled clinical trial that enrolled 129 patients with advanced GIST who had received prior treatment with other FDA-approved targeted therapies, imatinib, sunitinib and regorafenib. The trial compared patients who were randomized to receive Qinlock to patients who were randomized to receive placebo, to determine whether progression free survival (PFS) – the time from initial treatment in the clinical trial to growth of the cancer or death – was longer in the Qinlock group compared to the placebo group. During treatment in the trial, patients received Qinlock or placebo once a day in 28-day cycles, repeated until tumor growth was found (disease progression), or the patient experienced intolerable side effects. After disease progression, patients who were randomized to placebo were given the option of switching to Qinlock.

On average, the PFS rate in patients in the Qinlock group was 6.3 months, compared to one month for patients in the placebo group.

Safety

ADVERSE EVENTS

The most common adverse reactions (≥20%) were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmarplantar erythrodysesthesia, and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥4%) were increased lipase and decreased phosphate.

WARNINGS & PRECAUTIONS

Palmar-Plantar Erythrodysesthesia Syndrome: Based on severity, withhold QINLOCK and resume at same or reduced dose.
New Primary Cutaneous Malignancies: Perform dermatologic evaluations when initiating QINLOCK and routinely during treatment.
Hypertension: Do not initiate QINLOCK in patients with uncontrolled hypertension and monitor blood pressure during treatment. Based on severity, withhold QINLOCK and then resume at same or reduced dose or permanently discontinue.
Cardiac Dysfunction: Assess ejection fraction by echocardiogram or MUGA scan prior to initiating QINLOCK and during treatment, as clinically indicated. Permanently discontinue QINLOCK for Grade 3 or 4 left ventricular systolic dysfunction.
Risk of Impaired Wound Healing: Withhold QINLOCK for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of QINLOCK after resolution of wound healing complications has not been established.
Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

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Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2, and BRAF.

Dose & Administration

ADULTS

The recommended dosage of QINLOCK is 150 mg orally once daily with or without food until disease progression or unacceptable toxicity at the same time each day.

PEDIATRICS

The safety and effectiveness of QINLOCK in pediatric patients have not been established.

GERIATRICS

Of the 85 patients in INVICTUS who received QINLOCK 150 mg orally once daily, 24% were between 65 to 74 years of age and 9% were 75 years of age or older. Clinical studies of QINLOCK did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

RENAL IMPAIRMENT

The effects of severe renal impairment (CLcr 15 to 29 mL/min) or moderate to severe hepatic impairment (total bilirubin >1.5 × ULN, AST any) on the pharmacokinetics of ripretinib have not been studied.

HEPATIC IMPAIRMENT

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin 1 to 1.5 × ULN and AST any). A recommended dosage of QINLOCK has not been established for patients with moderate or severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 50 mg.