Ripretinib (QINLOCK)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Ripretinib is a tyrosine kinase inhibitor.
- It inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase that includes wild type, primary, and secondary mutations.
- KIT primary mutations at exons 9 and 11 with secondary resistance mutations in exon 13 and 14, and primary or secondary mutations in exons 17 and 18 of the activation loop conformation-controlling switch region.
- It also inhibits PDGFRA primary exon 18 mutation D842V in the conformation-controlling switch region and exon 12 mutations in the auxiliary inhibitory switch.
- Ripretinib binds as an advanced type II kinase inhibitor that penetrates the embedded KIT/PDGFRA switch pockets.
- In vitro, ripretinib inhibits other kinase such as PDGFRB, TIE2, VEGFR2, and BRAF.

Indication(s) Under Review in This Document

- Treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Dosage Form(s) Under Review

- Tablets, 50 mg. Dose is 150 mg orally once daily with or without food.

Clinical Evidence Summary

Efficacy Considerations

- Efficacy data are summarized in Table 1 based on an Independent Review Committee.

RIPRETINIB in GIST

Table 1: Efficacy results from the INVICTUS (NCT03353753) Trial

Study	Study Design	Study Population	Treatment	Results
Blay, et al. INVICTUS (NCT03353753) Phase III, double-blind, randomized, placebo-controlled Funded by Deciphera Pharmaceuticals	Inclusion ▪ Diagnosis of gastrointestinal stromal tumor ▪ At least one measurable lesion according to mRECIST 1.1 ▪ Progressed on at least imatinib, sunitinib, and regorafenib, or documented intolerance to any of these treatments despite dose modifications ▪ *KIT* and *PDGFRA* mutation and WT ▪ M/F ≥18 years old ▪ ECOG 0 to 2 Exclusion ▪ Anticancer treatment within 14 days of study drug or 5x the half-life ▪ Receiving adjuvant cancer treatment ▪ LVEF <50%, NYHA II to IV, active ischemia, or other uncontrolled cardiac condition ▪ VTE within 3 months prior to first dose ▪ Arterial thrombotic or embolic event within 6 months of first dose	Median Age = 59 yo Male = 55% White = 75% ECOG 0 = 44% 1 or 2 = 56% Primary Mutation *KIT* exon 9 = 17% *KIT* exon 11 = 55% Other *KIT* = 2% *PDGFRA* = 4% *KIT* and *PDGFRA* WT = 8% Not available = 14% Previously treated = 85 3 prior therapies = 64% 4-7 prior therapies 36%	Ripretinib 150 mg once daily + BSC vs. placebo + BSC 1º Endpoint PFS 2º Endpoint ORR (CR + PR)	N = 85 (Ripretinib) N = 44 (Placebo) **Primary Endpoint** **PFS / Ripretinib / Placebo / HR** Med PFS (months) (95% CI): 6.3 (4.6-6.9) / 1.0 (0.9-1.7) / 0.15 (0.09-0.25); P<0.0001 6 month PFS %: 51 (39.4-61.4) / 3.2 (0.2-13.8) / N/A **Response / Ripretinib / Placebo / P-value** ORR % (95% CI): 9.4% (4.2-17.7) / 0% (33-55) / 0.0504 CR: 0% (0-4) / 0% (0-8) PR: 9% (4-18) / 0% (0-8) Med OS (months) (95% CI): 15.1 (12.3-15.1) / 6.6 (4.1-11.6) / 0.36 (0.21-0.62) 6 month OS %: 84.3 (74.5-90.6) / 55.9 (39.9-69.2) / N/A Median DOR: NR / - / - ▪ Median follow-up = 6.3 months ▪ EORTC QLQ-C30 = trouble with strenuous activity, trouble taking short or long walk, needing help with ADLs ▪ EQ-VAS = report of overall health

ADL = activities of daily living; M/F = male or female; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Groups; GIST = gastrointestinal stromal tumor; OR = overall response; ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DOR = duration of response; PFS = medium progression-free survival; EORTC = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS = EuroQol visual analogue scale; HR = hazard ratio

- Study Design and Intervention
  - Eligible patients with confirmed gastrointestinal stromal tumors with at least 3 prior lines of therapy that includes imatinib, sunitinib, and regorafenib.
  - Patients were randomized 2:1 to receive ripretinib 150 mg by mouth daily or placebo.
  - Upon disease progression, treatment will be unblinded
    - Patients randomized to ripretinib 150 mg by mouth daily will either continue ripretinib at an increased dose of 150 mg by mouth twice daily, continue at the same dose, or discontinue the drug.
    - Patients randomized to placebo will either cross over to receive ripretinib 150 mg by mouth daily or discontinue the study.
    - Patients who cross over to ripretinib 150 mg by mouth daily and progress will either continue ripretinib at an increased dose of 150 mg by mouth twice daily, continue at the same dose, or discontinue the drug.
- Sub-Group Analysis of Study Population
  - In the subgroup analysis, ripretinib was clinically favored in patients who were ≥75 years old, white/Caucasian, male/female, ECOG 1 or 2, and had at least 3 lines of prior therapy.
- Results
  - Median follow-up = 6.3 months
  - Median duration of response = not reached
  - Primary Endpoint (Ripretinib vs Placebo)
    - Median PFS = 6.3 months vs 1 month
  - Secondary Endpoint
    - Median OS = 15.1 months vs 6.6 months
      - Patients who had disease progression on placebo were allowed to crossover to receive ripretinib. In patients who crossed over to ripretinib, mOS = 11.6 months versus 1.8 months in patients who did not cross over.
    - ORR = 9.4% vs 0%
      - All responses were partial and no patients had complete response
      - 66% had SD at 6 weeks and 47% had SD at 12 weeks
      - 19% had progressive disease
  - Scores for Global Functioning
    - EORTC-QLQ-C30 from baseline to cycle 2 day 1 was stable with adjusted mean change in score of 3.5 (95% CI; −3.4 to 10.5) for role functioning and 1.6 (−2.5 to 5.7) for physical functioning.
    - EQ-VAS from baseline to cycle 2 on day 1 also remained stable with adjusted mean change in scores of 3.7 (95% CI; −1.1 to −8.6).

Safety Considerations

- Most common side effect reported in ≥Grade 3 treatment-related treatment-emergent adverse events was increase lipase increase (5%), hypertension (4%), fatigue (2%), and hypophosphataemia (2%).
- Summary of safety data is summarized in Table 2 regarding grade 3-4 adverse events.

Table 2: Safety results from INVICTUS (NCT03353753) Trial

Study	Results	Comments
Blay, et al. INVICTUS (NCT03353753) Phase III, double-blind, randomized, placebo-controlled	Common Grade 3-4 lab abnormality (≥4%) = increased lipase and decreased phosphate Serious adverse events = 9% AEs leading to discontinuation = 4.7% AEs leading to dose interruption/modification = 14.1% Deaths due to AE = 1.2% ▪ Death = 1.2% ▪ Pulmonary edema = 0% ▪ Septic shock = 0%	▪ Most common adverse effect was alopecia = 49% (Grade 1-2) ▪ AEs leading to discontinuation (4.7%) was due to cardiac failure, death of unknown cause, general physical health deterioration, and palmar-plantar erythrodysesthesia. ▪ AEs leading to dose interruption/modification (14.1%) was due to nausea, increased bilirubin, and PPES

PPES = palmar-plantar erythrodysesthesia syndrome

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**:
    - Palmar-Plantar Erythrodysesthesia Syndrome (PPES): occurred in 21% of patients with 1.2% of patients discontinuing treatment, dose interruption in 2.4% of patients, and dose reduction in 1.2% of patients. Based on severity, withhold ripretinib and resume at same or reduced dose.
    - New Primary Cutaneous Malignancies: occurred in 4.7% of patients with cutaneous squamous cell carcinoma and keratoacanthoma occurring in 7% and 1.9% respectively in the pooled safety population. Patients should be advised to immediately report any change in or development of new skin lesions.
    - Hypertension: 14% of patients experienced Grade 1 to 3 hypertension where 7% specifically experienced Grade 3 hypertension. Ripretinib should not be started in uncontrolled hypertension and should be adequately controlled prior to starting.
    - Cardiac Dysfunction: occurred in 1.2% of patients and 1.7% of patients when looking at the pooled safety analysis that included cardiac dysfunction (e.g. cardiac failure, acute left ventricular failure, diastolic dysfunction, and ventricular hypertrophy). Cardiac dysfunction led to dose discontinuation in 3.4% of patients and who had baseline and at least one post-baseline echocardiogram. Ejection fraction should be assessed by an ECHO or MUGA prior to initiating ripretinib and should be discontinued if Grade or 4 left ventricular systolic dysfunction occur.
    - Risk of Impaired Wound Healing: ripretinib can impair wound healing by inhibiting the vascular endothelial growth factor (VEGF) signaling pathway. Withhold ripretinib at least 1 week prior to elective surgery and do not administer for at least 2 weeks following surgery or until wound is healed.
    - Embryo-Fetal Toxicity: advise women on potential risk to fetus and to use effective contraception during treatment and for at least 1 week after the final dose.

- **Adverse reactions**
    - **Common** (≥20%): alopecia, palmar-plantar erythrodysesthesia, fatigue, nausea, diarrhea, and myalgia
    - **Serious Adverse events / Deaths / Discontinuation:** anemia, cardiac failure, death of unknown cause, dyspnea, fecaloma, GERD, hyperkalemia, hypophosphatemia, nausea, and upper GI hemorrhage.
        - Death occurred in 1.2%
        - Discontinuation in 4.7%
        - Dose interruptions in 14.1%
        - Dose reductions in 5.9%

Other Considerations

- Drug-Drug Interactions
    - Strong CYP3A4 Inhibitors: coadministration with a strong CYP3A4 inhibitor increases exposure of ripretinib and its active metabolite (DP-5439), which can increase risk of adverse effects. Monitor frequently during use for adverse reactions.
    - Strong CYP3A4 Inducers: coadministration with a strong CYP3A4 inducer decreases exposure of ripretinib and its active metabolite (DP-5439), which may decrease the antitumor effect of ripretinib. Avoid concomitant use with a strong CYP3A4 inducer.
- Pregnancy: no available data in pregnancy. Based on animal studies, fetal harm occurred in pregnant rats and rabbits when exposed to ripretinib causing malformations associated with cardiovascular and skeletal system, anatomic variations, reduced fetal body weight, and increased post-implantation loss at maternal exposure at the recommended dose of 150 mg. Advise pregnant and those who are planning to be pregnant on potential fetal risk prior to starting ripretinib.
- Lactation: no available data regarding secretion of ripretinib or its metabolites in human milk or its effect on breastfed infants or milk production. Advise patients not to breastfeed during treatment with ripretinib and for one week after the final dose.
- Geriatric use: No clinically important differences were seen between ≥65 years old and younger in terms of safety and efficacy.
- Renal/hepatic function: not studied in CrCl <30 mL/min and moderate to severe hepatic impairment. No dose modifications recommended in patients with mild or moderate renal impairment (CrCl 30 to 89 mL/min) and mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin 1 to 1.5 x ULN and AST any).
- Metabolism: primarily metabolized by CYP3A4. One circulating plasma metabolite (DP-5439) has been identified.
- Excretion: after a single oral dose of ripretinib 150 mg, 34% will be recovered in feces and 0.02% in the urine. Six percent of circulating metabolite DP-5439 will be recovered in feces and 0.1% in the urine.

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** PFS = 6.3 vs. 1.0 mos; ripretinib vs. placebo, respectively
- **Effect Size:** HR = 0.15 (95% CI 0.09-0.25); P<0.0001 for PFS
- **Potential Harm (>20%):** Moderate
    - (Grade 1-2) Alopecia, myalgia, nausea, fatigue, palmar–plantar erythrodysesthesia, and diarrhea
- **Net Clinical Benefit:** Moderate

Other Therapeutic Options

Alternative treatments for advanced GIST are listed in table 3.

Table 3: Treatment Alternatives for GIST[1,5-7]

Drug	Formulary status	Clinical Guidance	Other Considerations
Ripretinib Blay, et al.	TBD	NCCN v1.2022: 150 mg daily preferred 4L therapy (cat 1) 5L+: Dose escalation to 150 mg BID if previously treated with 150 mg daily (cat 2A)	▪ 4th drug therapy for GIST ▪ mPFS = 6.3 months ▪ ORR = 9.4% ▪ Monitor blood pressure and assess cardiac function prior to starting therapy ▪ DDI with strong CYP3A4 inducer and inhibitor
Sorafenib Montemurro, et al.	PA-F	NCCN v1.2022: Useful in certain circumstances after approved therapies (cat 2A)	▪ Off-label use ▪ Fourth-line setting after use of imatinib, sunitinib, and nilotinib ▪ mPFS = 7.1 months ▪ mOS = 11 months ▪ Sorafenib was moderately tolerated with dose reductions occurring in a third of patients. Toxicity was reported in 56% of patients with most common being skin toxicity (38%)
Nilotinib Reichardt P, et al.	NF	NCCN: Useful in certain circumstances after approved therapies (cat 2A)	▪ Off-label use ▪ P3 following prior imatinib and sunitinib, nilotinib vs. BSC similar PFS (109 vs. 111 days)
Pazopanib Mir, et al.	NF	NCCN: Useful in certain circumstances after approved therapies (cat 2A)	▪ Off-label use ▪ P2 following prior imatinib and sunitinib, pazopanib + BSC vs. BSC, improved mPFS 3.4 vs. 2.3 months ▪ Toxicity high with gr ≥ 3 events in 72%

F = formulary; NF = non-formulary; GIST = gastrointestinal stromal tumors; ORR = overall response rate; PFS = progression-free survival; DOR = duration of response; OS = overall survival; RCC = renal cell carcinoma; pNET = pancreatic neuroendocrine tumor; CR = complete response; PR = partial response; Ph+ = Philadelphia chromosome; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; ASM = aggressive systemic mastocytosis; HES = hypereosinophilic syndrome; CEL = chronic eosinophilic leukemia; DFSP = dermatofibrosarcoma protuberans; CRC = colorectal cancer; HCC = hepatocellular carcinoma, PDGFRA = platelet-derived growth factor receptor alpha

Projected Place in Therapy[1,3-4]

- Gastrointestinal stromal tumors (GIST) is an uncommon mesenchymal cancer that occurs in the gastrointestinal (GI) system. It comprises of less than 1% of all GI tract tumors and occurs in 7 to 10 cases per million each year.
- Historically, GIST was seen to be highly resistant to cytotoxic chemotherapy with poor prognosis in patients with metastatic or unresectable disease. However, the discovery of the activating mutations of the *KIT* gene introduced the use of tyrosine kinase inhibitors (TKI) such imatinib for the management of GIST.
- Ripretinib is a switch control TKI that broadly inhibits *KIT* (exon 9, 11, 13, 14, 17, and 18) and *PDGFRA* (exon 18, including D842V resistance mutation) kinase signaling through dual mechanism of action. The dual action mechanism provides broad inhibition of KIT and PDGFRA kinase activity by binding to the switch pocket and activation loop to lock the kinase into its inactive state leading to cell proliferation.
- Guidelines
    - NCCN: For patients with GIST, ripretinib is the preferred fourth-line therapy agent in patients who have had three prior regimens that includes imatinib.
    - UpToDate: For patients with GIST (irrespective of D842V mutation status) who have progressed on or intolerant to three or more TKIs, including imatinib.
- Ripretinib is a switch control TKI that was approved based on durable progression free survival. Patients with GIST who have been on prior therapies currently have limited options for subsequent lines of therapy after progression or intolerance to three prior lines of therapy. Ripretinib should be available in the fourth line setting for patients with confirmed GIST who have progressed or intolerable to three prior lines that includes imatinib.

References

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