quizartinib (Vanflyta®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO284

Description

Quizartinib (Vanflyta) is an orally administered selective type II FLT3 inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
quizartinib (Vanflyta)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with 7+3 induction and cytarabine consolidation	17.7 mg tablets	60 tablets/30 days
		26.5 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Quizartinib (Vanflyta)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of **Newly diagnosed acute myeloid leukemia (AML)** when the following are met:
      1. The member has FLT3-ITD mutation-positive AML; **AND**
      2. Medication will not be used in combination with any other oncolytic medication with the exception of the therapies outlined below:
         i. Standard 7+3 induction (cytarabine and daunorubicin/idarubicin)
         ii. Cytarabine consolidation therapy; **AND**
      3. The member has received no prior therapy for AML

II. Quizartinib (Vanflyta) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia in the absence of FLT3 mutation
   B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
   C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
   D. Myelodysplastic syndrome (MDS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **OR**
   - Member has been established on induction therapy via an inpatient setting; **AND**
     i. Provider attests that the member initiated quizartinib (Vanflyta) as part of standard 7+3 induction therapy (cytarabine and daunorubicin/idarubicin) for AML; **AND**
     ii. Quizartinib (Vanflyta) will be used in combination with cytarabine consolidation therapy; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., achieved complete remission (CR)].

Supporting Evidence

I. Quizartinib (Vanflyta) is a selective type II FLT3 inhibitor studied in combination with chemotherapy as a once daily oral tablet for the treatment of *FLT3*-ITD-positive acute myeloid leukemia (AML). The efficacy and safety of quizartinib (Vanflyta) has not been established in pediatric patients.

II. An estimated 25% of newly diagnosed AML cases have *FLT3*-ITD mutations which are associated with a higher rate of relapse and poorer clinical outcomes as compared to wild type *FLT3* and *FLT*-TKD mutations. However, long-term impact of *FLT3*-ITD mutations on AML prognosis remains unclear. Given the complexities related to diagnosis treatment and management of AML, treatment in this disease space must be initiated by or in consultation with a specialist, such as an oncologist or hematologist.

III. Intensive induction therapy [e.g., cytarabine and an anthracycline (7+3) in combination with midostaurin (Rydapt)] followed by post-remission consolidation therapy [high dose cytarabine (HiDAC) + midostaurin (Rydapt)] and/or allogenic HCT (allo-HCT) in eligible patients has been the standard of care in FLT3-mutated AML. Post induction and consolidation, NCCN recommends maintenance therapy with an FLT3 inhibitor.

IV. Quizartinib (Vanflyta) was studied in a randomized, multi-center, double-blind, placebo-controlled, phase 3 trial of 539 patients with newly diagnosed FLT3-ITD mutated AML (QuANTUM-First). Trial participants (N=539) aged 20 to 75 were randomized 1:1 to receive either a standard 7 + 3 induction therapy with quizartinib (Vanflyta) or placebo, followed by consolidation with HiDAC plus quizartinib (Vanflyta) or placebo, and/or allo-HCT. This was then followed by maintenance with single agent quizartinib (Vanflyta) or placebo.

V. The efficacy of quizartinib (Vanflyta) was assessed via overall survival and event free survival (EFS) endpoints. Overall survival in the ITT population was longer with quizartinib (Vanflyta) than

placebo (31·9 months, 95% CI 21·0 – NE vs 15·1 months,13·2 – 26·2; HR 0·774, 0·614 – 0·975; p=0·032). In the population censored for allo-HCT OS also favored quizartinib (Vanflyta) (20·8 months, 95% CI 14·3 – 28·9 vs 12·9 months, 9·2 – 14·7; HR 0·752, 0·75, 0·56–1·01; p=0.055). The key secondary endpoint of EFS per the FDA's definition was not statistically significant (p= 0.24). However, per original protocol with a 56-day cutoff the results did gain statistical significance. In the induction treatment failure (ITF) population not achieving CRc remission by the end of induction up to day 56 quizartinib (Vanflyta) was found to be 11.9 months (8·1 – 16·5) as compared to 5.7 months (0·3 – 3·42) in the placebo group (HR 0·72, 95% CI 0·592 – 0·897; pnominal=0·0031). Median duration of complete remission was longer with quizartinib (Vanflyta) than with placebo (38·6 months, 95% CI 21·9–NE vs 12·4 months, 8·8–22·7; HR 0·62, 0·45–0·86) and in patients with complete remission during induction, relapse-free survival was longer with quizartinib (Vanflyta) compared to placebo (39·3 months, 95% CI 22·6–NE vs 13·6 months, 9·7–23·7; HR 0·61, 0·44–0·85).

VI. The quality of evidence is considered moderate. The clinical trial program for quizartinib (Vanflyta) consisted of a well-designed randomized clinical trial reporting positive results in overall survival, median duration of complete remission, and median relapse-free survival compared to intensive induction and consolidation therapies alone. However, protocol changes that shifted the definition of EFS may impact the FDA's review of quizartinib (Vanflyta). The effect of allo-HCT on OS and role of long-term quizartinib (Vanflyta) maintenance therapy after chemotherapy has yet to be fully reported. It is unknown how quizartinib (Vanflyta) will compare with other FDA approved medications in the newly diagnosed FLT3-mutated AML population.

VII. All trial participants experienced mild to moderate adverse events (AE) with similar AE profile between arms as both groups received 7 + 3 induction and HiDAC consolidation therapies. The most common AEs reported for quizartinib (Vanflyta) vs placebo included febrile neutropenia (44% vs 42%), pyrexia (42% vs 41%), diarrhea (37% vs 35%), hypokalemia (35% vs 36%), and nausea (34% vs 31%). Distinguishable side effects included QTc prolongation in 14% of the quizartinib (Vanflyta) patients vs 4% in the placebo group.

VIII. Quizartinib (Vanflyta) treatment led to a 34% dose interruption rate in clinical trials and a 19% dose reduction rate due to intolerable AEs. Dose reductions due to QTc prolongation were seen in 4% of quizartinib (Vanflyta) patients. Adverse events associated with a fatal outcome occurred in 30 participants (11%) in the quizartinib (Vanflyta) group and 26 (10%) in the placebo group, infections being the most common cause. Two patients (0.8%) treated with quizartinib (Vanflyta) had a cardiac arrest, with recorded ventricular fibrillation in the setting of severe hypokalemia.

IX. The use of quizartinib (Vanflyta) has not been studied in combination with medications other than 7 + 3 induction and consolidation chemotherapies. Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

Investigational or Not Medically Necessary Uses

I. Quizartinib (Vanflyta) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Acute myeloid leukemia in the absence of FLT3 mutation
   B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
   C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
   D. Myelodysplastic syndrome (MDS)

References

1. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Apr 25]. Lancet. 2023;S0140-6736(23)00464-6.
2. National Comprehensive Cancer Network. Acute Myeloid Leukemia. NCCN. April 5, 2023. Accessed May 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
3. Induction therapy for acute myeloid leukemia in medically-fit adults. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed May 5, 2023. https://www.uptodate.com/
4. Vanflyta. Package insert. Daiichi Sankyo Company, Ltd.; 2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Liver Carcinoma
	Advanced Renal Cell Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Advanced Soft Tissue Sarcoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
gilteritinib (XOSPATA®)	Relapse/Refractory FLT3 AML

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2023