Pharmacy Policy Bulletin: J-0897 FLT3 Kinase Inhibitors – Commercial and Healthcare Reform	
Number: J-0897	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes with Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0897-009	**Original Date:** 06/04/2003
Effective Date: 04/25/2025	**Review Date:** 04/09/2025

Drugs Product(s):	• Rydapt (midostaurin) • Vanflyta (quizartinib) • Xospata (gilteritinib)

FDA-Approved Indication(s):	• Rydapt (midostaurin)
	  ○ Treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 (*FLT3*) mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
	  ○ Treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
	• Vanflyta (quizartinib)
	  ○ In combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is *FLT3* internal tandem duplication (ITD)-positive as detected by an FDA-approved test.
	• Xospata (gilteritinib)
	  ○ Treatment of adult patients who have relapsed or refractory (R/R) AML with an *FLT3* mutation as detected by an FDA-approved test.

Background:	• Rydapt is a multi-targeted inhibitor of multiple receptor tyrosine kinases, including *FLT3* and *KIT*, which inhibit receptor signaling and cell proliferation, and induces cell apoptosis in leukemic cells. • Vanflyta inhibits FLT3 kinase activity, which prevents autophosphorylation of the receptor and inhibition of downstream *FLT3* receptor signaling and blockade of *FLT3-ITD*-dependent cell proliferation. ○ In clinical trials, induction phase therapy included on days 1-7 cytarabine 100 mg/m^2/day; days 1-3 daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day; then on days 8-21 oral Vanflyta.

- In clinical trials, consolidation phase therapy included on days 1, 3, and 5 HiDAC every 12 hours for a total of six doses; then on days 6-19, oral Vanflyta.

- Xospata is a small molecule that inhibits multiple receptor tyrosine kinases, including *FLT3*. Xospata demonstrated the ability to inhibit *FLT3* receptor signaling and proliferation in cells exogenously expressing *FLT3* including *FLT3-ITD*, tyrosine kinase domain mutations (TKD) *FLT3-D835Y* and *FLT3-ITD-D835Y*, and it induced apoptosis in leukemic cells expressing *FLT3-ITD*.
- Mutations of the *FLT3* gene occur in approximately 30% of all AML cases, with the ITD representing the most common type of *FLT3* mutation. *FLT3-ITD* is a common driver mutation that presents with a high leukemic burden and indicates poor prognosis in patients with AML.
- SM includes indolent SM, SM-AHN, ASM, and MCL. SM is usually caused by mutations in the *KIT* gene, and is characterized by mast cells accumulating in internal tissues and organs such as the liver, spleen, bone marrow, and small intestines.
- Prior authorization is utilized to ensure appropriate diagnosis by an FDA-approved test (e.g., LeukoStrat CDx FLT3 Mutation Assay). For additional information regarding FDA-approved companion diagnostics, please visit: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools
- Prescribing Considerations:
  - Tyrosine kinase inhibitors should be prescribed under the supervision of a hematologist or oncologist.
  - Rydapt
    - Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML.
  - Vanflyta
    - Vanflyta carries a black box warning for QT prolongation, torsades de pointes, and cardiac arrest.
    - Vanflyta is subject to a Risk Evaluation and Mitigation Strategies (REMS) program.
    - Vanflyta is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation; improvement in overall survival with Vanflyta in this setting has not been demonstrated.
  - Xospata
    - Xospata carries a black box warning for differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, it is recommended to initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Approval Criteria

I. Initial Authorization

A. Rydapt (midostaurin) (ICD-10: C92.0, C92.4, C92.5, C.92.6, C92.A, C96.21, D47.02, C94.3)
When a benefit, coverage of Rydapt may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member is 18 years of age or older.

2. The member meets one (1) of the following criteria **(a. or b.):**

a. The member has newly diagnosed acute myeloid leukemia (AML) and meets all of the following criteria **(i. and ii.):**

i. The member will be using Rydapt in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy regimens.

ii. The member is *FLT3* mutation-positive, as detected by an FDA approved test.

b. The member has a diagnosis of one (1) of the following **(i., ii., or iii.):**

i. Aggressive systemic mastocytosis (ASM)

ii. Systemic mastocytosis with associated hematological neoplasm (SM-AHN)

iii. Mast cell leukemia (MCL)

B. Vanflyta (quizartinib)

When a benefit, coverage of Vanflyta may be approved when all of the following criteria are met **(1. through 4.):**

1. The member is 18 years of age or older.

2. The member has newly diagnosed acute myeloid leukemia (AML, ICD-10: C92).

3. The member meets one (1) of the following criteria **(a., b., or c.):**

a. The member is receiving induction therapy and is using Vanflyta in combination with standard cytarabine and anthracycline induction therapy.

b. The member is receiving consolidation therapy and is using Vanflyta in combination with standard cytarabine consolidation therapy.

c. The member is receiving maintenance therapy and is using Vanflyta as monotherapy.

4. Disease is *FLT3-ITD*-positive as detected by an FDA-approved test.

C. Xospata (gilteritinib) (ICD-10: C92.02, C92.52, C92.62, C.92.A2)

When a benefit, coverage of Xospata may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older.

2. The member has a diagnosis of relapsed or refractory acute myeloid leukemia (AML).

3. The member is *FLT3* mutation-positive, as detected by an FDA approved test.

II. Reauthorization:

When a benefit, reauthorization of an FLT3 kinase inhibitor may be approved when the following criterion is met **(A.)**:

A. The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as one (1) of the following **(1. or 2.)**:

1. Disease improvement

2. Delayed disease progression

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

IV. Coverage of oncology medications listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

Note: For previous versions please see policy J-0699 and policy J-0851

References:

1. Rydapt [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp, May 2023.
2. Vanflyta [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; June 2024.
3. Xospata [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; January 2022.
4. NCCN Guidelines. Systemic Mastocytosis v.3.2024 National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf. Accessed February 12, 2025.
5. NCCN Guidelines. Acute Myeloid Leukemia v.2.2025. National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed February 12, 2025.
6. Daver N., et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Nature News. Available at: https://www.nature.com/articles/s41375-018-0357-9. Accessed February 12, 2025.
7. U.S Food & Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed February 12, 2025.