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Revised: 11/15/19

Subject: Gilteritinib (Xospata®) Tablet

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DESCRIPTION:

Gilteritinib (Xospata) is an oral tyrosine kinase inhibitor (TKI) approved by the Food and Drug Administration (FDA) in November 2018 for “the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.” Gilteritinib was previously granted orphan designation by the FDA for the treatment of AML in July 2017. Gilteritinib inhibits multiple receptor tyrosine kinases including AXL and FLT3. Inhibition of FLT3 receptor signaling and cell proliferation induces apoptosis in leukemic cells expressing mutant FLT3 receptors or overexpressing wild type FLT3 and PDGF receptors. Gilteritinib is the second drug to be approved by the FDA for the treatment of FLT3 mutation-positive AML. The other drug is midostaurin (Rydapt) approved in April 2017, but it differs from gilteritinib in that midostaurin is indicated for newly-diagnosed AML only (as of October 2019). In addition, midostaurin is considered a “first-generation” FLT3 inhibitor that targets numerous other tyrosine kinases (e.g., PKC, c-KIT, PDFRβ, VEGFR1/2, etc.). Gilteritinib is a “second-generation” FLT-3 inhibitor with greater FLT3 specificity than midostaurin. Of note, sorafenib (Nexavar) is an oral multitarget TKI that has been used off-label for FLT3-mutated AML. Sorafenib primarily inhibits RAF-1 but also has FLT3 inhibitory activity.

Acute myeloid leukemia is a hematological malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults, and accounts for the largest number of annual deaths from leukemia in the US. A diagnosis is typically made based on the presence of 20% or more myeloid blast in the marrow or peripheral blood. Assessment of molecular abnormalities (KIT, FLT3, NPM1, CEBPA, IDH1, IDH2, TP53, and other mutations) has become important for risk assessment, prognostication, and treatment selection. The most common AML mutation is in the FLT3 gene. The FLT3 gene encodes a receptor tyrosine kinase involved in hematopoiesis. Two major classes of activating FLT3 mutations have been identified in patients with AML; internal tandem duplications (ITD), ~30% of AML patients, and tyrosine kinase domain (TKD) point mutations, ~10% AML patients. Patients with a FLT3-ITD mutation, as opposed to wild-type FLT3, typically have shorter remission durations, higher relapse rates, and poorer survival outcomes. Patients with a FLT3-TKD mutation may also have worse outcomes, but the risk

impact is less clear. Treatment of AML is divided into induction chemotherapy and postremission (e.g., consolidation) therapy. Initial treatment decisions are primarily based on age (<60 or ≥60), history of prior myelodysplasia or cytotoxic therapy, and performance status. Candidates for intensive remission induction therapy typically receive a regimen based on a backbone of cytarabine plus an anthracycline (daunorubicin or idarubicin). Up to two courses of inpatient induction therapy may be attempted to induce a complete response. If a complete response is achieved, consolidation therapy normally consists of cytarabine for 3 or 4 cycles (inpatient or outpatient). An allogeneic hematopoietic stem cell transplantation (HSCT) can be considered for induction failures and as a consolidation option for patients with unfavorable-risk cytogenetics and/or molecular abnormalities. For patients with relapsed/refractory FTL3-mutated AML, gilteritinib is an available treatment option. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for AML (Version 2.2020) list single-agent gilteritinib as a category 1 treatment option for patients with relapsed/refractory FTL3-mutated AML (includes both FLT3-TKD and FLT3-ITD mutations). The guidelines also list hypomethylating agents [azacitidine (Vidaza) or decitabine (Dacogen)] + sorafenib as a category 2A treatment option for relapsed/refractory AML with a FLT3-ITD mutation. In general, the NCCN recommends enrollment in a clinical trial as the strongly preferred option for patients with relapsed/refractory AML.

The efficacy and safety of gilteritinib leading to FDA approval was assessed in an interim analysis of the ADMIRAL trial (NCT02421939), which included 138 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. Gilteritinib was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. Dose reductions were allowed, to manage adverse events, and dose increases were allowed, to increase clinical benefit. Efficacy was established by the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 4.6 months. The majority of included patients were currently experiencing an untreated relapse (59%) and were transfusion-dependent at baseline (77%). A total of 27 patients (20%) had a prior stem cell translation. FLT3 mutation status was ITD alone in 88%, TKD alone in 9%, and both ITD and TKD in 4%. Treatment with gilteritinib resulted in a CR/CRh rate of 29/138 (21%) with a median duration of response (DOR) of 4.6 months [CR – 11.6% (DOR – 8.6 months), CRh – 9.4% (DOR – 2.9 months)]. Of the 106 patients that were red blood cell transfusion dependent and/or platelet transfusion dependent at baseline, 17 (31.1%) patients required no transfusions during any 56-day post-baseline period. Of note, no responses occurred in the 12 patients with FLT3-TKD only. The most common Grade 3 or higher toxicities included pneumonia, sepsis, increased transaminases, and dyspnea. Refer to the product labeling (package inset) for more detailed information on adverse effects.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of gilteritinib (Xospata) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “4”):

1. **EITHER** of the following (“a” or “b”):

a. **ALL** of the following ("i", "ii", and "iii"):
   i. Member has a confirmed diagnosis of acute myeloid leukemia (AML)
   ii. Gilteritinib is being used as second-line or later therapy for relapsed or refractory disease
   iii. Gilteritinib will be used as single-agent therapy (i.e., not used in combination with other chemotherapy)

b. Other FDA-approved or NCCN supported diagnosis when **ONE** of the following is met ("i" or ii"):
   i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
   ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

2. Member has FLT3 (FMS-like tyrosine kinase 3) mutation-positive disease – laboratory documentation of a FLT3-ITD (internal tandem duplication) or FLT3-TKD (tyrosine kinase domain) mutation must be submitted [i.e., ratio of mutant to wild-type alleles of at least 0.05]
3. Member has not previously experienced disease progression during active treatment with a FLT3 inhibitor (e.g., midostaurin, sorafenib)
4. The dosage of gilteritinib does not exceed 120 mg (three 40 mg tablets) once daily

Approval duration: 6 months

Continuation of gilteritinib (Xospata) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. An authorization or reauthorization for gilteritinib has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of FLT3 mutation-positive AML or other FDA-approved or NCCN-supported diagnosis, **OR** the member has previously met **ALL** indication-specific criteria
2. The member has not experienced disease progression during treatment with gilteritinib
3. For AML indication only - gilteritinib is being used as a single-agent therapy (i.e., not used in combination with other chemotherapy)
4. The dosage of gilteritinib does not exceed 120 mg (three 40 mg tablets) once daily

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test
  - Select patients for the treatment of AML based on the presence of FLT3 mutations in the blood or bone marrow

- The recommended starting dose is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.
- Assess blood counts and blood chemistries, including creatine phosphokinase, prior to initiation at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles.

Dose Adjustments

- Treatment-Related Toxicity
  - Differentiation Syndrome - if differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. Resume gilteritinib when signs and symptoms improve to Grade 2 or lower.
  - Posterior Reversible Encephalopathy Syndrome – discontinue gilteritinib
  - QT Prolongation
    - QTc >500 msec - interrupt treatment, and then resume at 80 mg when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec
    - QTc interval increased by >30 msec on ECG on day 8 of cycle 1 - confirm with ECG on day 9, and, if confirmed, consider dose reduction to 80 mg
  - Pancreatitis - interrupt treatment until pancreatitis is resolved and then resume at 80 mg
  - Other Grade 3 or higher Toxicity - interrupt treatment until toxicity resolves or improves to Grade 1, and then resume at 80 mg
- Hepatic Impairment - specific guidelines for dosage adjustments in mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment are not available; it appears that no initial dosage adjustments are needed. Gilteritinib has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).
- Renal Impairment - specific guidelines for dosage adjustments in mild (creatinine clearance (CrCl) of 50 to 80 mL/min) or moderate (CrCl of 30 to 50 mL/min) renal impairment are not available; it appears that no initial dosage adjustments are needed. Gilteritinib has not been evaluated in patients with severe renal impairment (CrCl of 29 mL/min or less).

Drug Availability

- 40 mg tablets in 90-count bottles

PRECAUTIONS:

Boxed Warning

- **WARNING: DIFFERENTIATION SYNDROME**
  - Patients treated with Xospata have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Contraindications

- Patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

Precautions/Warnings

- **Differentiation Syndrome**: Of 319 patients treated with gilteritinib in the clinical trials, 3% experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with gilteritinib included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after gilteritinib initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of gilteritinib. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt gilteritinib until signs and symptoms are no longer severe
- **Posterior reversible encephalopathy syndrome (PRES**): Of 319 patients treated with gilteritinib in the clinical trials, 1% experienced PRES with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue in patients who develop PRES.
- **Prolonged QT Interval**: Use has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce dosage in patients who have a QTcF >500 msec. Correct hypokalemia or hypomagnesemia prior to and during administration.
- **Pancreatitis**: Of 319 patients treated in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose in patients who develop pancreatitis.
- **Embryo-Fetal Toxicity**: Based on findings in animals and its mechanism of action, gilteritinib can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose.
- **Drug Interactions**: Concomitant use of gilteritinib with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease efficacy. Avoid concomitant use with combined P-gp and strong CYP3A inducers. Concomitant use of gilteritinib with a strong CYP3A inhibitor increases gilteritinib exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for adverse reactions. Interrupt and reduce dosage in patients with serious or life-threatening toxicity. Concomitant use of gilteritinib may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs unless their use is considered essential for the care of the patient.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnoses Codes That Support Medical Necessity

C92.00	Acute myeloblastic leukemia not having achieved remission
C92.02	Acute myeloblastic leukemia in relapse
C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.52	Acute myelomonocytic leukemia in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia in relapse
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.02	Acute monoblastic/monocytic leukemia in relapse
C94.00	Acute erythroid leukemia not having achieved remission
C94.02	Acute erythroid leukemia in relapse
C94.20	Acute megakaryoblastic leukemia not having achieved remission
C94.22	Acute megakaryoblastic leukemia in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Refractory AML: Inability to achieve a complete response (CR) following induction chemotherapy.

Relapsed AML: Following a complete response the reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause.

RELATED GUIDELINES:

Midostaurin (Rydapt), 09-J2000-86

Sorafenib (Nexavar) Tablets, 09-J1000-50

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 10/09/19.

GUIDELINE UPDATE INFORMATION:

03/15/19	New Medical Coverage Guideline.
11/15/19	Review and revision to guidelines consisting of updating the description, position statement, dosage/administration, precautions, and references.