**09-J3000-27**

**Original Effective Date: 03/15/19**

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**Revised: 11/15/19**

# Subject: Glasdegib (Daurismo®) Tablet

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Glasdegib (Daurismo) is an oral hedgehog pathway inhibitor approved by the Food and Drug Administration (FDA) in November 2018 and is indicated “in combination with low-dose cytarabine for the treatment of newly-diagnosed acute myelogenous leukemia (AML) in patients who are 75 years or older or who have comorbidities that make them ineligible for intensive induction chemotherapy”. Glasdegib works by binding to and inhibiting the transmembrane protein smoothened (SMO) that is necessary for hedgehog signal transduction. A greater inhibition in tumor size and a reduced number of CD45-positive and CD33-positive blasts in the bone marrow were observed with glasdegib plus low-dose cytarabine compared with glasdegib or low-dose cytarabine alone in a murine xenotransplant model of human AML. Two other hedgehog pathway inhibitors are available in the US; vismodegib (Erivedge) FDA approved in January 2012 and sonidegib (Odomzo) FDA approved in July 2015. Unlike glasdegib, both of these drugs are FDA approved for metastatic or locally advanced basal cell carcinoma only (as of February 2019). Glasdegib was previously granted orphan designation by the FDA for the treatment of AML in June 2017. Glasdegib, as sponsored by the innovator drug company, also has an orphan designation for the treatment of myelodysplastic syndrome (October 2017).

Acute myeloid leukemia (AML) 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. 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). The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for AML (Version 2.2020) list glasdegib + low-dose cytarabine as a category 2A recommended treatment option for patients 60 years of age or older and who are not

candidates for intensive remission induction therapy or decline intensive therapy. NCCN includes a footnote stating “This regimen is for treatment of newly-diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (i.e., severe cardiac disease, ECOG performance status ≥2, or baseline creatine >1.3 mg/dL”. Other listed regimens (all category 2A) for patients without specific mutations or other unique characteristics include: lower-intensity therapy (5-azacytadine, decitabine, or low-dose cytarabine); venetoclax + decitabine, azacitidine, or low-dose cytarabine; and best supportive care (hydroxyurea, transfusion support). Glasdegib + low-dose cytarabine is also recommended as post-induction therapy in these same patients if they had a positive clinical response to glasdegib + low-dose cytarabine induction. The guidelines also include a Category 2A recommendation for use in relapsed/refractory AML as a component of repeating the initial successful induction regimen if late relapse (≥12 months since induction regimen) if not administered continuously and not stopped due to development of clinical resistance.

The safety and efficacy of glasdegib leading to FDA approval was evaluated in the multicenter, open-label, randomized BRIGHT AML 1003 trial (NCT01546038) in 132 patients with newly-diagnosed AML (n=116) or high-risk myelodysplastic syndrome (MDS) RAEB-2 (refractory anemia with excess blasts 2) (n=16). Patients in this study were 55 years of age or older and met at least one of the following criteria: age 75 years or older, severe cardiac disease (e.g., left ventricular ejection fraction <45%), a baseline ECOG performance status of 2, or a baseline serum creatinine level greater than 1.3 mg/dL. Patients were randomized 2:1 to receive glasdegib 100 mg daily with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle or cytarabine alone in 28-day cycles until disease progression or unacceptable toxicity. Since the MDS subgroup did not show a statistically significant difference in overall survival between the treatment groups (glasdegib + low-dose cytarabine - 10.9 months vs. low-dose cytarabine – 10.3 months), this data is NOT included in the product labeling/package insert, and the information below only applies to the 115 AML patients cited in the labeling. Of note, due to the small sample size, more patients with MDS are being assessed an expansion study (NCT02367456) to better understand the impact of glasdegib in MDS patients.

The median age on the AML patients was 77 years and 61% of patients were 75 years of age or older. A total of 71 patients (62%) had baseline severe cardiac disease, 59 (51%) had an ECOG performance status of 2, and 20 (17%) had a baseline serum creatinine level greater than 1.3 mg/dL. Efficacy was established on the basis of overall survival (OS) from the date of randomization to death from any cause. The median duration of treatment in the glasdegib + low-dose cytarabine arm was 83 days (range 3 to 972 days), and the median duration of treatment in the low-dose cytarabine alone arm was 47 days (range 6 to 239 days). Thirty-two patients (38%) were treated with glasdegib + low-dose cytarabine for at least 6 months and 14 patients (17%) were treated for at least 1 year. At a median follow-up time of about 20 months, the OS time was significantly improved by 4 months in patients who received glasdegib + low-dose cytarabine vs. low-dose cytarabine alone (8.3 months vs. 4.3 months; HR=0.46; 95% CI, 0.3 to 0.71; p=0.0002). Combination therapy also increased the complete response rate [18.2% (n=14) vs. 2.6% (n=1)]. Serious adverse reactions were reported in 79% of patients treated in the glasdegib + low-dose cytarabine arm. The most common (≥5%) serious adverse reactions were febrile neutropenia (29%), pneumonia (23%), hemorrhage (12%), anemia (7%), and sepsis (7%). Dose reductions associated with adverse reactions were reported in 26% of patients, and the most common reasons (≥2%) for dose reductions due to adverse reactions were muscle spasms (5%), fatigue (4%), febrile neutropenia (4%), anemia (2%), thrombocytopenia (2%), and ECG QT prolonged (2%). Adverse reactions leading to permanent discontinuation were reported in 36% of patients treated, and the most common (≥2%) reasons for permanent discontinuation were pneumonia (6%), febrile neutropenia (4%), sepsis (4%), sudden death (2%), myocardial infarction (2%), nausea (2%), and renal insufficiency (2%).

## 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 glasdegib (Daurismo) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. **ANY** of the following ("a", "b", or "c"):
    a. Member has newly-diagnosed acute myeloid leukemia (AML) [includes de novo AML, AML evolving from myelodysplastic syndrome (MDS) or other antecedent hematological disorder (AHD), and AML after previous cytotoxic therapy or radiation (i.e., secondary AML)], and **ALL** of the following ("i" to "iii"):
        i. Use is for **EITHER** of the following ("1" or "2"):
            1. Initial treatment induction
            2. Post-induction therapy following previous induction therapy with glasdegib + low-dose cytarabine, **AND** the member had a positive clinical response to glasdegib + low-dose cytarabine
        ii. **EITHER** of the following ("1" or "2"):
            1. Member is 75 years of age or older
            2. Member has one or more significant comorbidities that preclude use of intensive induction chemotherapy (e.g., severe cardiac disease, baseline serum creatinine level greater than 1.3 mg/dL, baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater) – the specific comorbidity(ies) must be provided
        iii. Glasdegib will be used in combination with low-dose subcutaneous cytarabine (i.e., 20 mg twice daily on days 1 to 10 of each 28-day cycle)
    b. Member has relapsed or refractory AML, and **ALL** of the following:
        i. Glasdegib is being used as a component of repeating the initial successful induction regimen
        ii. Member has a late relapse (defined as ≥12 months since induction regimen)
        iii. Glasdegib was not administered continuously and not stopped due to development of clinical resistance
    c. 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. Dosage of glasdegib does not exceed 100 mg once daily, and will be obtained using the fewest number of tablets possible

**Approval duration**: 6 months

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

1. An authorization or reauthorization for glasdegib (Daurismo) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of 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 glasdegib
3. For AML indication only - glasdegib will be used in combination with low-dose subcutaneous cytarabine (i.e., 20 mg twice daily on days 1 to 10 of each 28-day cycle)
4. Dosage of glasdegib does not exceed 100 mg once daily, and will be obtained using the fewest number of tablets possible

**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**

- Indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. Limitation of Use (per package labeling): Glasdegib has not been studied in patients with the comorbidities of severe renal impairment or moderate-to-severe hepatic impairment.
    - The recommended dose is 100 mg orally once daily on days 1 to 28 in combination with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle in the absence of unacceptable toxicity or loss of disease control. For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response.
    - Assess complete blood counts, electrolytes, renal, and hepatic function prior to initiation and at least once weekly for the first month. Monitor electrolytes and renal function once monthly for the duration of therapy. Obtain serum creatine kinase levels prior to initiation and as indicated clinically thereafter (e.g., if muscle symptoms are reported). Monitor electrocardiograms (ECGs) prior to initiation, approximately one week after initiation, and then once monthly for the next two months to assess for QTc prolongation. Repeat ECG if abnormal. Certain patients may require more frequent and ongoing ECG monitoring.

**Dose Adjustments**

- Treatment-Related Toxicity:
    - QT Prolongation (on at least 2 separate ECGs)
        - QTc interval >480 to 500 ms – assess electrolyte levels and supplement as clinically indicated. Review and adjust concomitant medications with known QTc interval-prolonging effects. Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation to less than or equal to 480 ms.
        - QTc interval >500 ms – assess electrolyte levels and supplement as clinically indicated. Review and adjust concomitant medications with known QTc interval-prolonging effects. Interrupt DAURISMO. Resume DAURISMO at a reduced dose of 50 mg once daily when

QTc interval returns to within 30 ms of baseline or less than or equal to 480 ms. Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. Consider re-escalating the dose of DAURISMO to 100 mg daily if an alternative etiology for the QTc prolongation can be identified.

- QTc interval prolongation with life-threatening arrhythmia - discontinue glasdegib permanently

- Hematologic Toxicity:
  - Platelets less than 10,000 cells/mcL for more than 42 days in the absence of disease - discontinue glasdegib and low-dose cytarabine permanently
  - Neutrophil count less than 500 cells/mcL for more than 42 days in the absence of disease - discontinue glasdegib and low-dose cytarabine permanently
- Nonhematologic Toxicity:
  - Grade 3 - interrupt glasdegib and/or low-dose cytarabine until symptoms reduce to mild or return to baseline. Resume glasdegib at the same dose level, or at a reduced dose of 50 mg. Resume low-dose cytarabine at the same dose level, or at a reduced dose of 15 mg or 10 mg. If toxicity recurs, discontinue glasdegib and low-dose cytarabine. If toxicity is attributable to glasdegib only, low-dose cytarabine may be continued.
  - Grade 4 - discontinue glasdegib and low-dose cytarabine permanently

- Hepatic Impairment - specific guidelines for dosage adjustments in mild hepatic impairment are not available; it appears that no initial dosage adjustments are needed. Glasdegib has not been evaluated in patients with moderate to severe hepatic impairment.
- Renal Impairment - specific guidelines for dosage adjustments in mild or moderate renal impairment are not available; it appears that no initial dosage adjustments are needed. Glasdegib has not been evaluated in patients with severe renal impairment.

**Drug Availability**

- 25 mg tablets in 60-count bottle
- 100 mg tablets in 30-count bottle

## PRECAUTIONS:

**Boxed Warning**

- **WARNING: EMBRYO-FETAL TOXICITY**
  - Daurismo can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Daurismo is embryotoxic, fetotoxic, and teratogenic in animals.
  - Conduct pregnancy testing in females of reproductive potential prior to initiation of Daurismo treatment. Advise females of reproductive potential to use effective contraception during treatment with Daurismo and for at least 30 days after the last dose.
  - Advise males of the potential risk of Daurismo exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with Daurismo and for at least 30 days after the last dose to avoid potential drug exposure.

**Contraindications**

- None

**Precautions/Warnings**

- **Embryo-Fetal Toxicity**: based on its mechanism of action and findings from animal embryo-fetal developmental toxicity studies, glasdegib can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus.
    - Females of Reproductive Potential - not recommended for use during pregnancy. Conduct pregnancy testing in female patients of reproductive potential prior to initiating treatment. Advise females of reproductive potential to use effective contraception during treatment and for at least 30 days after the last dose. Advise women not to breastfeed during treatment and for at least 30 days after the last dose.
    - Males - advise male patients with female partners of the potential risk of exposure through semen and to use effective contraception, including a condom, even after vasectomy, to avoid drug exposure to a pregnant partner or a female partner of reproductive potential during treatment and for at least 30 days after the last dose
    - Blood Donation - advise patients not to donate blood or blood products while taking glasdegib and for at least 30 days after the last dose because their blood or blood products might be given to a female of reproductive potential
- **QTc Interval Prolongation**: patients treated with glasdegib can develop QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia. Of the 98 evaluable patients treated with glasdegib 100 mg in combination with low-dose cytarabine in the clinical trial, 5% were found to have a QTc interval greater than 500 ms and 4% of patients had an increase from baseline QTc greater than 60 ms. The clinical trial excluded patients with baseline QTc of greater than 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring is recommended. Avoid co-administration of QTc prolonging drugs. Discontinue glasdegib permanently for patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.
- **Drug Interactions:**
    - Strong CYP3A Inhibitor - co-administration with strong CYP3A inhibitors increased glasdegib plasma concentrations which may increase the risk of adverse reactions including QTc interval prolongation. Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment or monitor patients for increased risk of adverse reactions including QTc interval prolongation.
    - Strong CYP3A Inducers - co-administration with strong CYP3A inducers decreased glasdegib plasma concentrations which may reduce efficacy. Avoid co-administration with strong CYP3A4 inducers.
    - QTc Prolonging Drugs - co-administration with QTc prolonging drugs may increase the risk of QTc interval prolongation. Avoid co-administration of QTc prolonging drugs with glasdegib or replace with alternative therapies. If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation

## 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

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|---|---|
| C92.00 – C92.02 | Acute myeloblastic leukemia |
| C92.50 – C92.52 | Acute myelomonocytic leukemia |
| C92.60 – C92.62 | Acute myeloid leukemia with 11q23-abnormality |
| C92.A0 – C92.A2 | Acute myeloid leukemia with multilineage dysplasia |
| C93.00 – C92.02 | Acute monoblastic/monocytic leukemia |
| C94.00 – C94.02 | Acute erythroid leukemia |
| C94.20 – C94.22 | Acute megakaryoblastic leukemia |

## 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 guideline creation.

## 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:

**Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01**

**Azacitidine (Vidaza) Injection, 09-J0000-84**

**Enasidenib Mesylate (Idhifa) Tablet, 09-J2000-90**

**Venetoclax (Venclexta) Tablet, 09-J2000-64**

## OTHER:

None

## REFERENCES:


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7. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 9/23/19.
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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:

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|---|---|
| 03/15/19 | New Medical Coverage Guideline. |
| 11/15/19 | Review and revision to guidelines consisting of updating the description, position statement, billing/coding, and references. |