PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDAURISMO®

Glasdegib Tablets

Tablet, 25 mg and 100 mg glasdegib (as glasdegib maleate), Oral

Antineoplastic Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	[01/2022]
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dose Adjustment	[01/2022]
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DAURISMO (glasdegib) is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed and previously untreated acute myeloid leukemia (AML) in adult patients who are age ≥75 years or who are not eligible to receive intensive induction chemotherapy.

Distribution Restrictions

DAURISMO is only available through a control distribution program called the DAURISMO Pregnancy Prevention Program (DPPP). Under this program, only prescribers and pharmacies registered with the program are able to prescribe and dispense the product, respectively. In addition, DAURISMO can only be dispensed to patients who are registered and meet all the conditions of the DPPP. For more information, please contact the DPPP at 1 844 616-6888.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of DAURISMO in the pediatric population have not been established. Adverse changes in growing bone, including premature partial to complete closure of the epiphyseal plate were observed in non-clinical toxicity studies. DAURISMO is not indicated for use in the pediatric population.

1.2 Geriatrics

Geriatrics (> 65 years of age): In the clinical studies of DAURISMO with low-dose cytarabine, 98% of the patients were age 65 years or older and 60% of the patients were age 75 years or older.

2 CONTRAINDICATIONS

DAURISMO (glasdegib) is contraindicated in:

- Female patients who are pregnant (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1.1 WARNINGS AND PRECAUTIONS, Special Populations, *Pregnant Women***).
- Breastfeeding female patients (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1.1 WARNINGS AND PRECAUTIONS, Special Populations, *Breast-feeding***).
- Female patients of childbearing potential who do not comply with effective contraceptive measures (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1 WARNINGS AND PRECAUTIONS, Special Populations, *Females of Childbearing Potential***).
- Male patients who do not comply with effective contraceptive measures (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1 WARNINGS AND PRECAUTIONS, Special Populations, *Male Patients***).
- Children and adolescents aged below 18 years. (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1.3 WARNINGS AND PRECAUTIONS, Special Populations, *Pediatrics***).
- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

DAURISMO (glasdegib) should be initiated and monitored only under the supervision of a physician qualified in the use of cancer therapies and with a full understanding of the risks of DAURISMO therapy and monitoring requirements.

- DAURISMO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. DAURISMO is embryotoxic, fetotoxic, and teratogenic in animals (see **CONTRAINDICATIONS**, and **WARNINGS AND PRECAUTIONS, Embryo-Fetal Toxicity**).
- 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 (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, *Females of Childbearing Potential***).
- 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 (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, *Male Patients***).
- DAURISMO has not been studied in pediatric patients. In non-clinical rat toxicity studies, DAURISMO resulted in premature fusion of the epiphyseal plate. DAURISMO is not indicated for use in the pediatric population (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, *Pediatrics***).
- DAURISMO is available only through a controlled distribution program called the DAURISMO Pregnancy Prevention Program (DPPP).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

CYP3A4 Inhibitors

Co-administration of DAURISMO (glasdegib) with strong CYP3A4 inhibitors increased glasdegib plasma concentrations. Increased glasdegib concentrations may increase the risk of adverse reactions including QTc interval prolongation (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**). Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO. Monitor patients for increased risk of adverse reactions including QTc interval prolongation (see **9.4 DRUG INTERACTIONS, Drug-Drug Interactions**).

CYP3A4 Inducers

Avoid co-administration of DAURISMO with strong CYP3A4 inducers. Co-administration of DAURISMO with strong CYP3A4 inducers decreased glasdegib plasma concentrations (see **9.4 DRUG INTERACTIONS, Drug-Drug Interactions).**

Avoid co-administration of DAURISMO with moderate CYP3A4 inducers. Co-administration of DAURISMO with moderate CYP3A inducers may decrease glasdegib plasma concentrations (see **4.2 Recommended Dose and Dosage Adjustment**, **9.4 DRUG INTERACTIONS, Drug-Drug Interactions**).

QTc Prolonging Drugs

Avoid co-administration of QTc prolonging drugs with DAURISMO or replace with alternative therapies. Co-administration of DAURISMO with QTc prolonging drugs may increase the risk of QTc interval

prolongation (see **7 WARNINGS AND PRECAUTIONS**, **Cardiovascular**, QT Interval Prolongation and **9.4 DRUG INTERACTIONS, Drug-Drug Interactions**). If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation (see **7 WARNINGS AND PRECAUTION**S, **Monitoring and Laboratory Test**).

Hepatic Impairment

No dose adjustments are recommended in patients with mild (total bilirubin ≤1 × upper limit of normal [ULN] and aspartate aminotransferase [AST] >1 × ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) hepatic impairment. Limited data are available in patients with moderate (n=3; total bilirubin > 1.5 to 3.0 x ULN and any AST) and severe hepatic impairment (n=1; total bilirubin >3.0 × ULN and any AST). Caution should be used in patients with moderate and severe hepatic impairment.

Renal Impairment

No dose adjustments are recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min). No data are available for glasdegib in patients with severe renal impairment (CrCl <30 mL/min) (see **10.3 CLINICAL PHARMACOLOGY**, ***Special Populations and Conditions, Renal Insufficiency***). Caution should be used in patients with severe renal impairment. No data are available in patients requiring hemodialysis.

Geriatric Population

No dose adjustment of DAURISMO in elderly (≥65 years of age) patients is required (see **10.3 CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, ***Geriatrics***).

No starting dose adjustments are required on the basis of patient age, race, gender, or body weight (see **10.3 CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of DAURISMO is 100 mg taken 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. Continue DAURISMO as long as the patient is deriving clinical benefit. For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response.

Dose Modifications

Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of DAURISMO should be reduced to 50 mg taken orally once daily.

Dose modification and management guidelines for specific adverse reactions are provided in Table 1 below.

Table 1 - DAURISMO Dose Modifications and Management Recommendations for Adverse Drug Reactions

Adverse Drug Reaction	Recommended Action and/or Dose Modification	
QTc interval prolongation on at least 2 separate electrocardiograms (ECGs)	QTc interval greater than 480 ms 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 interval greater than 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.
	QTc interval interval prolongation with life-threatening arrhythmia	Discontinue DAURISMO permanently.
Creatine Kinase (CK) Elevations and Muscle-Related Adverse Reactions	Grade 1* [CK elevation >ULN - 2.5 x ULN]	▪ Continue DAURISMO at the same dose level and monitor CK levels weekly until resolution to baseline and then monthly. Monitor muscle symptoms for changes until resolution to baseline. ▪ Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
	Grade 2* **without** renal impairment (serum Cr ≤ ULN) [CK elevation >2.5 x ULN - 5 x ULN]	▪ Interrupt DAURISMO and monitor CK levels weekly until resolution to baseline. ▪ Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume DAURISMO at the same dose level and monitor CK levels monthly thereafter. ▪ Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. ▪ If symptoms recur, interrupt DAURISMO until resolution to baseline. Re-introduce DAURISMO at 50 mg once daily and follow the same monitoring

Adverse Drug Reaction	Recommended Action and/or Dose Modification	
		recommendations. If symptoms persist, consider discontinuing DAURISMO.
	Grade 3 or 4* **without** renal impairment (serum Cr ≤ ULN) [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [Grade 4 (CK elevation >10 x ULN)]	▪ Interrupt DAURISMO and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. ▪ Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. ▪ If renal function is **not impaired** and CK resolves to baseline, consider resuming DAURISMO at 50 mg once daily. CK levels should be measured weekly for 2 months after re-administration of DAURISMO and monthly thereafter.
	Grade 2, 3 or 4 **with** renal impairment (serum Cr > ULN per CTCAE 4.0)	▪ If renal function is **impaired**, interrupt DAURISMO and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment. ▪ Monitor CK and serum creatinine levels weekly until resolution to baseline. ▪ Monitor muscle symptoms for changes until resolution to baseline. ▪ If CK and serum creatinine levels resolve to baseline, consider resuming DAURISMO at 50 mg once daily and measure CK levels weekly for 2 months and monthly thereafter; otherwise discontinue treatment permanently.
Hematologic toxicity	Platelets less than 10 Gi/L for more than 42 days in the absence of disease	Discontinue DAURISMO and low-dose cytarabine permanently.
	Neutrophil count less than 0.5 Gi/L for more than 42 days in the absence of disease	Discontinue DAURISMO and low-dose cytarabine permanently.

Adverse Drug Reaction	Recommended Action and/or Dose Modification	
Nonhematologic toxicity	Grade 3*	▪ Interrupt DAURISMO and/or low-dose cytarabine until symptoms reduce to mild or return to baseline. ▪ Resume DAURISMO 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 DAURISMO and low-dose cytarabine. ▪ If toxicity is attributable to DAURISMO only, low-dose cytarabine may be continued.
	Grade 4*	Withhold DAURISMO and/or low dose cytarabine until symptoms resolve to Grade ≤1 or return to baseline. Upon recovery, resume DAURISMO at a dose of 50 mg or discontinue treatment at the discretion of the prescriber.

*Grading according to CTCAE 4.0: Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events.

Dosage modification for Concomitant Use with Moderate CYP3A4 Inducers

Avoid concomitant use of DAURISMO with moderate CYP3A4 inducers. If concomitant use of moderate CYP3A4 inducers cannot be avoided, increase the DAURISMO dose as tolerated as shown in Table 2. After the moderate CYP3A4 inducer has been discontinued for 7 days, resume the DAURISMO dose taken prior to initiating the moderate CYP3A4 inducer (see **9.4 DRUG INTERACTIONS, Drug-Drug Interactions**).

Table 2 - Dose Modification Recommendations for DAURISMO with Concomitant Use of Moderate CYP3A4 Inducers

Current Dose	Adjusted Dose
100 mg orally once daily	200 mg orally once daily
50 mg orally once daily	100 mg orally once daily

4.4 Administration

DAURISMO may be taken with or without food.

Patients should be encouraged to take their dose at approximately the same time each day. If a dose of DAURISMO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due.

4.5 Missed Dose

If a dose of DAURISMO is missed or not taken at the usual time, the dose should be administered as soon as possible and at least 12 hours prior to the next scheduled dose. The normal schedule should be resumed the following day. Two doses of DAURISMO should not be administered within 12 hours.

5 OVERDOSAGE

There is no specific antidote for DAURISMO (glasdegib). Management of DAURISMO overdose should include symptomatic treatment and ECG monitoring.

Glasdegib has been administered in clinical studies up to a dose of 640 mg/day. At the highest dosage the adverse events reported were nausea, vomiting, dehydration, fatigue and dizziness.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 25 mg glasdegib (as glasdegib maleate) 100 mg glasdegib (as glasdegib maleate)	Dibasic calcium phosphate anhydrous, hypromellose, iron oxide yellow (25 mg tablet), iron oxide red and iron oxide yellow (100 mg tablet), lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate; titanium dioxide, triacetin

100 mg strength: pale orange film-coated tablet debossed with “Pfizer” on one side and “GLS 100” on the other side.

25 mg strength: yellow film-coated tablet debossed with “Pfizer” on one side and “GLS 25” on the other side.

Packaging: DAURISMO (glasdegib) is supplied as follows:

- 25 mg: Bottle containing 60 tablets
- 100 mg: Bottle containing 30 tablets

7 WARNINGS AND PRECAUTIONS

Please see **SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Cardiovascular

QT Interval Prolongation

Heart rate corrected QT (QTc) interval prolongation has been observed in patients treated with DAURISMO at greater than two-fold therapeutic dose (>270 mg). Ventricular arrhythmias, including

ventricular fibrillation and ventricular tachycardia, have been reported. In a thorough QT study in 36 healthy subjects treated with DAURISMO, at steady state therapeutic plasma concentrations (achieved with a 150 mg single dose), the largest mean QTc interval change was 8.03 msec (see **10.2 CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology**). In randomized study B1371003 (BRIGHT AML 1003), of patients with AML for which DAURISMO is not indicated, patients treated with DAURISMO 100 mg once daily with low-dose cytarabine, QTcF interval greater than 500 msec was reported in 6.0% of patients.

Driving and Operating Machinery

No studies on the effects of DAURISMO on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue while taking DAURISMO should exercise caution when driving or operating machinery.

Effects on Post-Natal Development

The safety and effectiveness of DAURISMO has not been established in pediatric patients. In repeat-dose toxicity studies in rats, oral administration of DAURISMO resulted in adverse changes in growing bone, teeth, and testis. Premature effects on bone consisted of partial to complete closure of the epiphyseal plate. Effects in growing incisor teeth included degeneration/necrosis of ameloblasts, and complete tooth loss with oral ulceration. Reproductive tissue toxicity was evidenced by testicular degeneration and hypospermatogenesis. These effects in bone, teeth and testis were observed after administration of DAURISMO for 26 weeks at greater than or equal to 50 mg/kg/day corresponding to approximately 8-times the steady state AUC in patients at the recommended human dose (see **2 CONTRAINDICATIONS, 16 NON-CLINICAL TOXICOLOGY, Repeat-Dose Toxicity** and **Reproductive Toxicity**).

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal embryo-fetal developmental toxicity studies, DAURISMO (glasdegib) can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. There is no clinical data on the use of DAURISMO in pregnant women. In animal embryo-fetal developmental toxicity studies, glasdegib caused embryotoxicity, fetotoxicity, and teratogenicity at exposures lower than the recommended human dose of 100 mg (see **16 NON-CLINICAL TOXICOLOGY, Developmental Toxicity**). Advise pregnant women of the potential risk to the fetus.

Females of Child-Bearing Potential (FCBP)

DAURISMO is contraindicated for use during pregnancy. A FCBP must not be given DAURISMO until pregnancy is excluded. Verify the pregnancy status of women of reproductive potential prior to initiating 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.

Breastfeeding is contraindicated during treatment with DAURISMO and for at least 30 days after the last dose (see **2 CONTRAINDICATIONS** and **7.1.2 WARNINGS AND PRECAUTIONS, Special Populations, *Breast-feeding***).

Males

Advise male patients with female partners of the potential risk of exposure through semen and to use effective contraception, including a condom with spermicide, even after vasectomy, to avoid drug exposure to a pregnant partner or a female partner of reproductive potential during treatment with DAURISMO for at least 30 days after the last dose (see **2 CONTRAINDICATIONS**).

Blood Donation

Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose of DAURISMO because their blood or blood products might be given to a female of reproductive potential.

Monitoring and Laboratory Tests

Assess complete blood counts, electrolytes, renal, and hepatic function prior to the initiation of DAURISMO and at least once weekly for the first month. Monitor electrolytes and renal function once monthly for the duration of therapy.

Creatine Kinase

Obtain serum creatine kinase (CK) levels prior to initiating treatment with DAURISMO and as indicated clinically thereafter (e.g., if muscle symptoms are reported). Manage any abnormalities promptly (see **4.2 Recommended Dose and Dosage Adjustment**).

ECG Monitoring

Monitor ECGs prior to the initiation of DAURISMO, 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 (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**, QT Interval Prolongation). Manage any abnormalities promptly (see **8 ADVERSE REACTIONS**).

Musculoskeletal

Muscle-related adverse reactions

In randomized study B1371003, muscle spasms were observed in 15% of patients treated with DAURISMO in combination with low-dose cytarabine (see **8.2 Clinical Trial Adverse Reactions**).

Inform all patients starting treatment with DAURISMO of the risk of muscle-related adverse reactions. Instruct them to report promptly any unexplained muscle pain, tenderness or weakness occurring during treatment with DAURISMO or if symptoms persist after discontinuing treatment.

Monitor serum CK levels prior to and during treatment with DAURISMO (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Management of high-grade CK elevation based on current standards of medical practice and following appropriate treatment guidelines is recommended. Follow dose modification or management recommendations (see **4.2 Recommended Dose and Dosage Adjustment).**

Reproductive Health: Female and Male Potential

- **Contraception in Men and Women**

  Based on its mechanism of action and findings from animal embryo-fetal developmental studies, DAURISMO can cause fetal harm when administered to a pregnant woman. Females of reproductive potential who are receiving this medication should use effective contraception during treatment with DAURISMO and for at least 30 days after the last dose (see **7.1 WARNINGS AND PRECAUTIONS, Special Populations, *Females of Childbearing Potential).***

  It is not known whether DAURISMO is present in semen. Advise males of the potential risk of exposure through semen and to use effective contraception, including a condom with spermicide, even after a vasectomy, to avoid drug exposure to a pregnant partner or a female partner of

reproductive potential during treatment with DAURISMO and for at least 30 days after the last dose (see **7.1 WARNINGS AND PRECAUTIONS, Special Populations, *Male Patients***).

- **Fertility**

  Based on nonclinical safety findings, DAURISMO has the potential to impair reproductive function in males. Some effects on male reproductive organs did not recover (see **16 NON-CLINICAL TOXICOLOGY**). Men should seek advice on effective fertility preservation before treatment. Based on its mechanism of action, DAURISMO may impair female fertility.

  In repeat-dose toxicity studies in rats, findings observed in the male reproductive tract included adverse testicular changes with DAURISMO at doses ≥50 mg/kg/day, and consisted of minimal to severe hypospermatogenesis characterized by partial to complete loss of spermatogonia, spermatocytes and spermatids and testicular degeneration. Hypospermatogenesis did not recover whereas testicular degeneration did recover. The dose at which adverse testicular effects were observed in male rats was identified as 50 mg/kg/day with corresponding systemic exposures that were approximately 8-times those associated with the observed human exposure at the 100 mg once daily dose (based on unbound AUC in respective species).

7.1 Special Populations

Females of Childbearing Potential

Females of childbearing potential must comply with effective contraceptive measures (see **2 CONTRAINDICATIONS**) to avoid becoming pregnant, as per the DAURISMO Pregnancy Prevention Program (DPPP). A FCBP must not be given DAURISMO until pregnancy is excluded. Verify the pregnancy status of female patients of reproductive potential prior to initiating treatment. If the patient becomes pregnant while taking DAURISMO, the patient should be apprised of the potential hazard to the fetus.

Criteria for FCBP

A FCBP is defined in the DPPP as a female patient who meets at least **one** of the following criteria:
- is menstruating,
- is amenorrhoeic and has not entered menopause (menopause should be clinically confirmed),
- is perimenopausal.

A female patient who does not meet one of the above criteria, has a XY genotype, Turner's syndrome, or uterine agenesis is defined as a Female of Non-Childbearing Potential.

For FCBP, DAURISMO is contraindicated unless **ALL** of the following conditions are met:

- The patient is willing and able to comply with the DPPP and all the conditions of use.
- If the patient is biologically capable of having children and is sexually active, the patient must agree to use two (2) highly effective methods of contraception consistently and correctly or to commit to continually abstaining from heterosexual contact.
- The patient has a consultation with a health care professional to discuss the **two** most appropriate simultaneous contraceptive methods to be used, and to instruct the patient in their consistent and correct use.
- The patient must be willing and able to comply with the pregnancy testing requirements noted in detail below; which includes a negative pregnancy test (blood or urine) within 7 days prior to

initiating DAURISMO treatment, as well as on-going monthly pregnancy tests throughout treatment.

- The patient is informed of the potential risk to a fetus.
- The patient understands the need to consult the health care professional immediately if the selected birth control methods are discontinued or if pregnancy is known or suspected.

Contraception

- FCBP (including those who normally do not use contraception due to a history of infertility and those who have amenorrhoea and have not entered menopause) must agree to use 2 highly effective methods of contraception consistently and correctly for the duration of the treatment period and for at least 30 days following discontinuation of DAURISMO.
- FCBP who chooses to abstain from heterosexual contact as a contraceptive measure must commit to using two methods of contraception at the same time if abstinence is no longer practiced.
- A FCBP who has amenorrhoea or has become amenorrhoeic must also use two effective methods of contraception simultaneously as outlined above.
- Female patients with a previous hysterectomy or bilateral oophorectomy are exempt from contraception use during DAURISMO therapy.
- FCBP must consult with a health care professional to discuss the most appropriate and effective contraceptive methods to be used.
- Acceptable forms of highly effective methods of contraception include:
  - abstinence,
  - established use of oral, injected or implanted hormonal methods of contraception,
  - correctly placed intrauterine device (IUD) or intrauterine system (IUS),
  - male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, suppository),
  - male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate,
  - bilateral tubal ligation or bilateral salpingectomy.

Pregnancy Testing

- Pregnancy must be excluded in a FCBP prior to initiating DAURISMO treatment.
- Even if abstinence is the chosen method of contraception, a pregnancy test (with sensitivity of at least 25 mIU/mL) must be conducted by a health care provider within 7 days prior to initiating DAURISMO treatment, and monthly during treatment.
- Additionally, pregnancy tests will be performed if a menstrual cycle is missed or when potential pregnancy is otherwise suspected.
- Dates and results for all pregnancy tests must be documented.

For FCBP, continuation of treatment will require a new prescription each month to allow for monthly pregnancy testing.

Pregnancy Reporting

- Patients must contact their health care provider immediately if pregnancy is suspected.
- If a patient becomes pregnant while taking DAURISMO, treatment must be immediately discontinued, and the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Report any suspected exposures to DAURISMO during pregnancy to Pfizer at 1-844-616-6888.

Fertility

Based on its mechanism of action, DAURISMO may impair female fertility.

Male Patients

- The patient must be willing and able to comply with the DPPP and all the conditions of use.
- The male patient must inform their female sexual partner that they are taking DAURISMO.
- The male patient must inform their female sexual partners of the potential serious risks to a developing fetus should she become pregnant during her male partner's course of treatment with DAURISMO, dose interruptions, and for at least 30 days following treatment discontinuation.

Contraception

- It is not known whether DAURISMO is present in semen. Advise males of the potential risk of exposure through semen and to use effective contraception, including a condom with spermicide, even after a vasectomy, to avoid drug exposure to a pregnant partner or a female partner of reproductive potential during treatment with DAURISMO, during dose interruptions, and for at least 30 days after the last dose.
- Your female partner of reproductive potential must also use a highly effective method of birth control for the duration of the male patient's treatment, and for at least 30 days after the last dose.

Semen Donation

Male patients must not donate semen during treatment with DAURISMO (including dose interruptions) and for at least 30 days following treatment discontinuation.

Pregnancy Reporting

- Male patients must contact their health care provider immediately if their female sexual partner may be pregnant.
- If a female sexual partner becomes pregnant following exposure to semen by a male patient taking DAURISMO, the female partner should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Report any suspected exposures to DAURISMO during pregnancy to Pfizer at 1-844-616-6888.

Fertility

DAURISMO may affect fertility in males. Male patients should seek advice from their health care professional on effective fertility preservation before treatment.

7.1.1 Pregnant Women

- DAURISMO is contraindicated for use during pregnancy.
- DAURISMO can cause fetal harm when administered to a pregnant female. Based on its mechanism of action and findings in animal embryo-fetal developmental toxicity studies, DAURISMO can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies using DAURISMO in pregnant women. The pregnancy status of women of reproductive potential should be established prior to initiating therapy.
- DAURISMO is embryotoxic, fetotoxic, and teratogenic in animals (see **16 NON-CLINICAL TOXICOLOGY, Developmental Toxicity**).

7.1.2 Breast-feeding

- Breastfeeding is contraindicated during treatment with DAURISMO.
- No studies have been conducted in humans to assess the effect of DAURISMO on milk production, its presence in breast milk, or its effects on the breastfed child. It is unknown whether of DAURISMO and its metabolites are excreted in human milk. Given the potential for serious adverse drug reactions in nursing infants from DAURISMO, females should not breastfeed during treatment with DAURISMO and for at least 30 days after the last dose (see **16 NON-CLINICAL TOXICOLOGY**).

7.1.3 Pediatrics

Pediatrics (≤18 years): The safety and efficacy of DAURISMO in pediatric patients has not been established. Non-clinical toxicity studies resulted in adverse changes in growing bone, teeth and testis (see **16 NON-CLINICAL TOXICOLOGY** and **2 CONTRAINDICATIONS**). Premature effects on bone consisted of partial to complete closure of the epiphyseal plate. Premature fusion epiphyses have occurred in pediatric patients treated with other hedgehog pathway inhibitors.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): In clinical study B1371003 of DAURISMO with low-dose cytarabine, 98% of the patients were aged 65 years or older and 60% of the patients were aged 75 years or older. The study did not include a sufficient number of patients younger than age 65 to determine differences in adverse drug reactions reported from patients older than 65 (see **14 CLINICAL TRIALS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of DAURISMO (glasdegib) is based on experience in study B1371003 (BRIGHT AML 1003) for 111 adults with newly diagnosed AML and 14 adults with high-risk myelodysplastic syndrome (high-risk MDS) for which DAURISMO is not indicated (see **14 CLINICAL TRIALS**). Patients were treated with DAURISMO 100 mg daily in combination with low-dose cytarabine (N=84) or low-dose cytarabine alone (N=41). The median duration of treatment in the DAURISMO with 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). The median exposure to DAURISMO in the DAURISMO with low-dose cytarabine arm was 76 days (range 3 to 954 days). The median average dose per cycle for

DAURISMO in the DAURISMO with low-dose cytarabine arm was 90 mg/day (range 19 to 101 mg/day). Thirty-two (32) patients (38%) were treated with DAURISMO with low-dose cytarabine for at least 6 months and 14 patients (17%) were treated for at least 1 year.

Serious adverse reactions were reported in 79% of patients treated in the DAURISMO with low-dose cytarabine arm. The most common (≥5%) serious adverse reactions in patients receiving DAURISMO with low-dose cytarabine 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 treated with DAURISMO with low-dose cytarabine, 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 with DAURISMO with low-dose cytarabine, 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%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reactions reported in the first 90 days of therapy in study B1371003 are shown in Table 4.

Table 4 - Adverse Reactions Occurring in ≥ 10% of Patients[a,b] Within the First 90 Days of Therapy in Study B1371003

Body System	Adverse Reactions	DAURISMO With Low-Dose Cytarabine N=84		Low-Dose Cytarabine N=41	
		All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %
Blood and lymphatic system disorder	Anemia	43	41	42	37
	Hemorrhage[c]	36	6	42	12
	Febrile neutropenia	31	31	22	22
	Thrombocytopenia	30	30	27	24
General disorders and administration site conditions	Fatigue[d]	36	14	32	7
	Edema[e]	30	0	20	2
	Mucositis[f]	21	1	12	0
	Pyrexia	18	1	22	2
	Chest pain[g]	12	1	2	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[h]	30	2	17	2
	Muscle spasm[i]	15	0	5	0
Gastrointestinal disorders	Nausea	29	1	12	2
	Constipation	20	1	12	0
	Abdominal pain[j]	19	0	12	0
	Diarrhea[k]	18	4	22	0

Body System	Adverse Reactions	DAURISMO With Low-Dose Cytarabine N=84		Low-Dose Cytarabine N=41	
		All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %
	Vomiting	18	2	10	2
Respiratory thoracic and mediastinal disorders	Dyspnea[l] Cough[m]	23 18	11 0	24 15	7 2
Metabolism and nutrition disorders	Decreased appetite	21	1	7	2
Nervous system disorders	Dysgeusia[n] Dizziness Headache	21 18 12	0 1 0	2 7 10	0 0 2
Skin and subcutaneous tissue disorders	Rash[o]	20	2	7	2
Infection and infestations	Pneumonia[p]	19	15	24	22
Investigations	Hyponatremia Platelet count decreased Weight decreased White blood cell count decreased	11 15 13 11	6 15 0 11	0 10 2 5	0 10 0 2
Cardiac disorders	Atrial arrhythmia[q]	13	4	7	2
Renal and urinary disorders	Renal insufficiency[r]	19	5	10	0

Abbreviations: N = number of patients.

Preferred terms were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Study B1371003 used National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Adverse reactions include events that commenced within 28 days after the last treatment dose.

[a.] Adverse reactions with ≥10% incidence in the DAURISMO with low-dose cytarabine arm or the low-dose cytarabine arm are included.

[b.] No Grade 5 events in the DAURISMO with low-dose cytarabine or low-dose cytarabine alone arm.

[c.] Hemorrhage includes petechiae, epistaxis, hematoma, contusion, rectal hemorrhage, anal hemorrhage, ecchymosis, gingival bleeding, hematuria, mouth hemorrhage, purpura, cerebral hemorrhage, eye contusion, eye hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematemesis, hemoptysis, hemorrhage, implant site hematoma, injection site bruising, retroperitoneal hematoma, thrombotic thrombocytopenic purpura, tracheal hemorrhage, conjunctival hemorrhage, disseminated intravascular coagulation, eyelid hematoma, hematochezia, hemorrhage intracranial, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, retinal hemorrhage, and subdural hematoma.

[d.] Fatigue includes asthenia and fatigue.

[e.] Edema includes edema peripheral, edema, fluid overload, fluid retention, and swelling face.

Body System	Adverse Reactions	DAURISMO With Low-Dose Cytarabine N=84		Low-Dose Cytarabine N=41	
		All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %

[f.] Mucositis includes mucosal inflammation, oropharyngeal pain, stomatitis, anal ulcer, gingival pain, laryngeal inflammation, esophagitis, oral pain, aphthous ulcer, mouth ulceration, and pharyngeal inflammation.
[g.] Chest pain includes chest pain and non-cardiac chest pain.
[h.] Musculoskeletal pain includes pain in extremity, arthralgia, back pain, myalgia, musculoskeletal pain, musculoskeletal chest pain, neck pain, and bone pain.
[i.] Muscle spasms includes muscle spasms and muscle tightness.
[j.] Abdominal pain includes abdominal pain, abdominal pain upper, and abdominal pain lower.
[k.] Diarrhea includes diarrhea, colitis, and gastroenteritis.
[l.] Dyspnea includes dyspnea, hypoxia, bronchospasm, and respiratory failure.
[m.] Cough includes cough and productive cough.
[n.] Dysgeusia includes dysgeusia and ageusia.
[o.] Rash includes rash, pruritus, erythema, skin ulcer, rash maculo-papular, and rash pruritic.
[p.] Pneumonia includes pneumonia, pneumonia aspiration, and lung infection.
[q.] Atrial arrhythmia includes atrial fibrillation, bradycardia, tachycardia, and sinus tachycardia.
[r.] Renal insufficiency includes acute kidney injury, blood creatinine increased, oliguria, and renal failure.

QT Interval Prolongation: (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular,** QT Interval Prolongation, and **10.2 CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology**).

8.3 Less Common Clinical Trial Adverse Reactions

Clinically-significant adverse reactions occurring in < 10% of patients treated with DAURISMO and low-dose cytarabine in study B1371003 include:

- Dental disorders: loose tooth and toothache
- Skin and subcutaneous tissue disorders: alopecia
- Cardiac disorders: QT interval prolonged

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Changes in selected post-baseline laboratory values that were observed in patients with newly diagnosed AML and other conditions for which DAURISMO is not indicated in the clinical trial are shown in Table 5.

Table 5 - Selected Laboratory Abnormalities (≥ 15%)[a] Within the First 90 Days of Therapy in Study B1371003

Laboratory Abnormality	DAURISMO with Low-Dose Cytarabine			Low-Dose Cytarabine		
	N	All Grades %	Grade 3 or 4* %	N	All Grades %	Grade 3 or 4* %
Creatinine increased	81	96	1	40	80	5
Hyponatremia	81	54	7	39	41	8
Hypomagnesemia	81	33	0	39	23	0
AST increased	80	28	1	40	23	0
Blood bilirubin increased	80	25	4	39	33	3
ALT increased	80	24	0	40	28	3
Alkaline phosphatase increased	80	23	0	40	28	3
Hyperkalemia	81	16	1	40	8	3
CPK increased	38	16	0	17	6	0
Hypokalemia	81	15	0	40	23	0

Abbreviations: N = number of patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CPK = creatine phosphokinase.
Study B1371003 used National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.
a. Maximum severity based on the number of patients with available on-study laboratory data.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

CYP3A4 inhibitors

Ketoconazole, a strong inhibitor of CYP3A4, dosed at 400 mg once daily for 7 days, increased the geometric mean area under the curve (AUC_{inf}) by ~140% and C_{max} by 40% of a single 200 mg oral dose of glasdegib in healthy volunteers. Use caution when administering concomitantly with strong CYP3A4 inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir or tipranavir) as an increase in glasdegib plasma concentration may occur. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended, if possible.

CYP3A4 inducers

Rifampin, a strong inducer of CYP3A4, administered at a dose of 600 mg once daily for 11 days, reduced the geometric mean AUC_{inf} by 70% and C_{max} by 35% of a single 100 mg dose of glasdegib in healthy volunteers. Avoid concomitant use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's Wort), as this may decrease glasdegib plasma

concentrations. Use caution with concomitant use of moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin), as they may also reduce glasdegib plasma concentrations.

Simulations using physiologic-based pharmacokinetic modeling suggested that coadministration of efavirenz (a moderate inducer of CYP3A4) with glasdegib decreased glasdegib AUC_{inf} by 55% and Cmax by 25%. Avoid concomitant use of moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin), as this may decrease glasdegib plasma concentrations. If concomitant use of moderate CYP3A4 inducers cannot be avoided, the dose of DAURISMO should be increased (see **4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

The drugs listed in Table 6 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 - Established or Potential Drug-Drug Interactions

Category/Common name	**Source of Evidence**	**Effect**	**Clinical comment**
Strong CYP3A4 Inhibitors Such as boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir or tipranavir	CT	Co-administration of DAURISMO (glasdegib) with strong CYP3A inhibitors increased glasdegib plasma concentrations. Increased glasdegib concentrations may increase the risk of adverse reactions including QTc interval prolongation (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).	Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO. Monitor patients for increased risk of adverse reactions including QTc interval prolongation (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).
Strong CYP3A Inducers Such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's Wort	CT	Co-administration of DAURISMO with strong CYP3A inducers decreased glasdegib plasma concentrations.	Avoid co-administration of DAURISMO with strong CYP3A4 inducers.
Moderate CYP3A Inducers (bosentan, efavirenz, etravirine, modafinil, nafcillin)	PK modelling	Co-administration of DAURISMO with moderate CYP3A inducers may decrease glasdegib plasma concentrations.	Avoid concomitant use of moderate CYP3A4 inducers

Category/Common name	**Source of Evidence**	**Effect**	**Clinical comment**
QTc Prolonging Drugs	CT	Co-administration of DAURISMO with QTc prolonging drugs may increase the risk of QTc interval prolongation (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).	Avoid co-administration of QTc prolonging drugs with DAURISMO or replace with alternative therapies. If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

In vitro studies of other CYP inhibition and induction

In vitro studies indicated that clinical drug-drug interactions as a result of glasdegib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 are unlikely to occur at clinically relevant concentrations. In vitro studies indicated that clinical drug-drug interactions as a result of glasdegib-mediated induction of the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A4 are unlikely to occur.

In vitro studies of UGT inhibition

In vitro studies indicated that clinical drug-drug interactions as a result of glasdegib-mediated inhibition of the metabolism of substrates for uridine-diphosphate glucuronosyltransferase (UGT)1A4, UGT1A6, UGT2B7, and UGT2B15 are unlikely to occur at clinically relevant concentrations. Glasdegib may have the potential to inhibit UGT1A1, and possibly UGT1A9 however, clinically relevant drug-drug interactions are not expected.

Gastric pH altering medicines:

Co-administration of a 100 mg glasdegib dose under fasted conditions with rabeprazole (a proton-pump inhibitor) did not alter glasdegib exposure and decreased C_{max} by 20%. Concomitant administration of glasdegib with acid-reducing agents (including PPIs, H_2-receptor antagonists, and locally-acting antacids) is not expected to result in clinically relevant interactions.

In vitro studies with drug transporters

In vitro studies indicated that clinical drug-drug interactions with concomitant medications that are substrates for P-glycoprotein (P-gp) systemically, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and multidrug and toxic compound extrusion (MATE)1 are unlikely to occur.

In vitro studies indicated that glasdegib may have the potential to inhibit breast cancer resistance protein (BCRP; systemically and at the gastrointestinal [GI] tract), P-gp (GI tract), (MATE)1 and MATE2K at clinically relevant concentrations.

9.5 Drug-Food Interactions

DAURISMO may be administered with or without food. The impact of food on the pharmacokinetics of glasdegib is not considered clinically relevant (see **10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption**).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Glasdegib is an inhibitor of the Hedgehog (Hh) signal transduction pathway that binds to Smoothened (SMO), a transmembrane protein. SMO stimulates the nuclear localization of Glioma-Associated Oncogene (GLI) transcription factors and induction of Hedgehog target genes. Glasdegib binding to SMO inhibits activity of SMO and blocks Hedgehog signaling. SMO is implicated in the maintenance of leukemic stem cell (LSC) dormancy and resistance to chemotherapy and targeted therapy.

10.2 Pharmacodynamics

Cardiac Electrophysiology: The effect of glasdegib administration on corrected QT interval (QTc) was evaluated in a randomized, single-dose, double-blind, 4-way crossover, placebo- and open-label moxifloxacin controlled study in 36 healthy subjects. At therapeutic plasma concentrations (achieved with a 150 mg single dose), the largest, placebo and baseline-adjusted QTc interval change was 8.03 msec (90% CI: 5.85, 10.22 msec). At approximately twice the therapeutic concentration (achieved with a 300 mg single dose), the QTc change was 13.43 msec (95% CI: 11.25, 15.61 msec). Moxifloxacin (400 mg), used as a positive control, showed a mean QTc change from baseline of 13.87 msec.

10.3 Pharmacokinetics

Absorption

Following a single 100 mg dose of glasdegib in patients, peak concentrations in plasma are rapidly reached with the median T_{max} of 2 hours. Following repeat 100 mg once daily dosing to steady state, glasdegib median T_{max} ranged from approximately 1.3 hours to 1.8 hours, in patients dosed with glasdegib in combination with low dose cytarabine.

After oral administration of glasdegib tablets, the mean absolute bioavailability is 77.12% (90% CI: 71.83%, 82.81%) compared to intravenous administration. Administration of a single 100 mg glasdegib dose with a high-fat, high-calorie meal (approximately total 800-1000 calories: 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) decreased exposure (AUC) by 16% and maximal concentrations (C_{max}) by 31%. The impact of food on the pharmacokinetics of glasdegib is not considered clinically relevant.

The steady state systemic glasdegib exposure (C_{max} and AUC_{tau}) increased in a dose proportional manner over the dosing range of 5 mg to 600 mg once daily. The median accumulation ratio of glasdegib ranged from 1.2 to 2.5 following once-daily dosing. At the 100 mg once daily glasdegib dose

given in combination with low dose cytarabine, the geometric mean (geometric coefficient of variation, % CV) of glasdegib C_{max} was 1252 ng/mL (44%) and AUC_{tau} was 17210 ng.hr/mL (54%).

Distribution

Glasdegib is 91% bound to human plasma proteins in vitro. The geometric mean (geometric %CV) apparent volume of distribution (Vz/F) was 188 (20) L following a single dose of 100 mg glasdegib in patients with hematologic malignancies.

Metabolism

The primary metabolic pathways for glasdegib were comprised of N-demethylation, glucuronidation, oxidation, and dehydrogenation. In vitro, CYP3A4 is responsible for the majority of parent depletion and contributed to the formation of other minor oxidative metabolites, with CYP2C8 and UGT1A9 playing a minor role in the metabolism of glasdegib.

In plasma, the N-desmethyl and N-glucuronide metabolites of glasdegib accounted for 7.9% and 7.2% of the circulating radioactivity, respectively. Other metabolites in plasma individually accounted for <5% of circulating radioactivity.

Elimination

The mean (± SD) plasma half-life of glasdegib was 17.4 ± 3.66 hours after a single dose of 100 mg glasdegib in patients with select hematologic malignancies. The geometric mean oral clearance after multiple dosing was 6.45 L/h. Following oral administration of a 100 mg radiolabeled dose of glasdegib to healthy subjects, mean 48.9% and 41.7% of the radioactivity dosed was recovered in urine and feces, respectively. The overall mean mass balance of the dosed radioactivity in the excreta was 90.6%. Unchanged glasdegib was the major component of human plasma, accounting for 69.4% of the total drug-related material. Unchanged glasdegib recovered in the urine and feces accounted for 17.2% and 19.5% of the dose, respectively.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of DAURISMO (glasdegib) in pediatric patients have not been established.
- **Geriatrics:** In patients assigned to treatment with DAURISMO with low-dose cytarabine (n=88; BRIGHT AML 1003, study B1371003), 97.7% of the patients were aged 65 or older and 60.2% of the patients were aged 75 or older. This study did not include a sufficient number of patients younger than age 65 to determine differences in adverse drug reactions reported from patients older than 65.
- **Sex:** Population pharmacokinetic analyses in patients (n=269) indicate that there are no clinically relevant effects of gender on the pharmacokinetics of glasdegib.
- **Pregnancy and Breast-feeding:** DAURISMO is contraindicated for use during pregnancy. Based on its mechanism of action and findings in animal embryo-fetal developmental toxicity studies, DAURISMO can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies using DAURISMO in pregnant women. Verify the pregnancy status of females of reproductive potential prior to initiating therapy (see **16 NON-CLINICAL TOXICOLOGY, Developmental Toxicity**).

  No studies have been conducted in humans to assess the effect of glasdegib on milk production, its presence in breast milk, or its effects on the breastfed child. It is unknown whether glasdegib and its metabolites are excreted in human milk. Given the potential for

serious adverse drug reactions in nursing infants from DAURISMO, breastfeeding is contraindicated during treatment with DAURISMO and for at least 30 days after the last dose (see **2 CONTRAINDICATIONS**).

- **Ethnic Origin:** Population pharmacokinetic analyses in patients (n=269) indicate that there are no clinically relevant effects of ethnic origin on the pharmacokinetics of glasdegib.
- **Hepatic Insufficiency:** Most clinical studies that were conducted excluded patients with AST or ALT >2.5 × ULN, or if due to underlying malignancy, >3.0 × ULN or with total bilirubin >2.0 × ULN. Based on a pooled population pharmacokinetic analysis, glasdegib clearance was not altered in patients with mild (n=43; total bilirubin ≤1 × ULN and AST >1 × ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST) hepatic impairment. No dose adjustments are recommended in patients with mild hepatic impairment. Insufficient data are available in patients with moderate (n=3; total bilirubin > 1.5 to 3.0 x ULN and any AST) and severe hepatic impairment (n=1; total bilirubin >3.0 × ULN and any AST).
- **Renal Insufficiency:** Following a 100 mg dose, 17.2% of glasdegib was recovered unchanged in the urine. Most clinical studies excluded patients with serum creatinine >1.5 × ULN or estimated CL_{cr} <60 mL/min.

  Results from a pooled population pharmacokinetic analysis indicate glasdegib clearance was not altered in patients with mild (n=102) renal impairment (60 mL/min≤CrCl<90 mL/min). While the clearance in patients with moderate (n=61) renal impairment (30 mL/min≤CrCl<60 mL/min) was numerically lower, it was not considered to be clinically relevant. No dose adjustments are recommended for patients with mild or moderate renal impairment. No data are available for glasdegib in patients with severe renal impairment (CrCl<30 mL/min). No data are available in patients requiring hemodialysis.
- **Obesity:** Population pharmacokinetic analyses in patients (n=269) indicate that there are no clinically relevant effects of body weight on the pharmacokinetics of glasdegib.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C.

The release of pharmaceuticals in the environment should be minimized. Any unused medicinal product or waste material should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name: glasdegib maleate

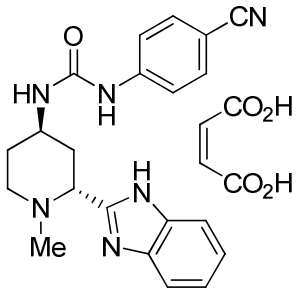
Chemical name: 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl) urea maleate

Molecular formula and molecular mass:

$C_{25}H_{26}N_6O_5$

490.51 Daltons

Structural formula:



Physicochemical properties: Glasdegib maleate is a white to pale colored powder with pKa values of 1.7 (benzimidazole nitrogen) and 6.1 (methylpiperidine nitrogen). The aqueous solubility of glasdegib maleate is 1.7 mg/mL.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of DAURISMO (glasdegib) in combination with low-dose cytarabine was evaluated in a multicenter, open-label, randomized study (BRIGHT AML 1003, study B1371003) in a total of 132 patients, which included 116 patients age 55 years or older with newly diagnosed AML who met at least one of the following criteria: a) age > 75 years, b) severe cardiac disease, c) baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, or d) baseline serum creatinine >1.3 mg/dL. Patients were randomized 2:1 to receive DAURISMO at a 100 mg daily dose with low-dose cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle (N=78) or low-dose cytarabine alone (N=38) in 28-day cycles until disease progression or unacceptable toxicity.

Patients were stratified by cytogenetic risk (good/intermediate or poor) at randomization.

The baseline demographic and disease characteristics are shown in Table 7.

Table 7 - Baseline Demographic and Disease Characteristics in Patients with AML

Demographic and Disease Characteristics	DAURISMO With Low-Dose Cytarabine (N=78)	Low-Dose Cytarabine Alone (N=38)
Demographics		
Age		
Median (Min, Max) (Years)	77 (64, 92)	76 (58, 83)
≥ 75 years N (%)	48 (62)	23 (61)
Sex, N (%)		
Male	59 (77)	23 (61)
Female	19 (24)	15 (39)
Race, N (%)		
White	75 (96)	38 (100)
Black or African American	1 (1)	0 (0)
Asian	2 (3)	0 (0)
Disease History, N (%)		
De Novo AML	38 (49)	18 (47)
Secondary AML	40 (51)	20 (53)
Prior Hypomethylating Agent Use	11 (14)	6 (16)
ECOG PS[a], N (%)		
0 to 1	36 (46)	20 (53)
2	41 (53)	18 (47)
Cytogenetic Risk Status, N (%)		
Good/Intermediate	49 (63)	21 (55)
Poor	29 (37)	17 (45)
Baseline Severe Cardiac Disease	52 (67)	20 (53)
Baseline Serum Creatinine >1.3 mg/dL	15 (19)	5 (13)

Abbreviations: AML = acute myeloid leukemia; N = number of patients; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

[a] Baseline ECOG PS was not reported for one patient in the DAURISMO with low-dose cytarabine arm.

14.2 Study Results

Efficacy in the overall study population was established on the basis of overall survival (OS) from the date of randomization to death from any cause. With a median follow-up of approximately 20 months, the DAURISMO with low-dose cytarabine arm was superior to low-dose cytarabine alone arm (Figure 1). The efficacy results are shown in Table 8.

Table 8 - Efficacy Results From Study B1371003

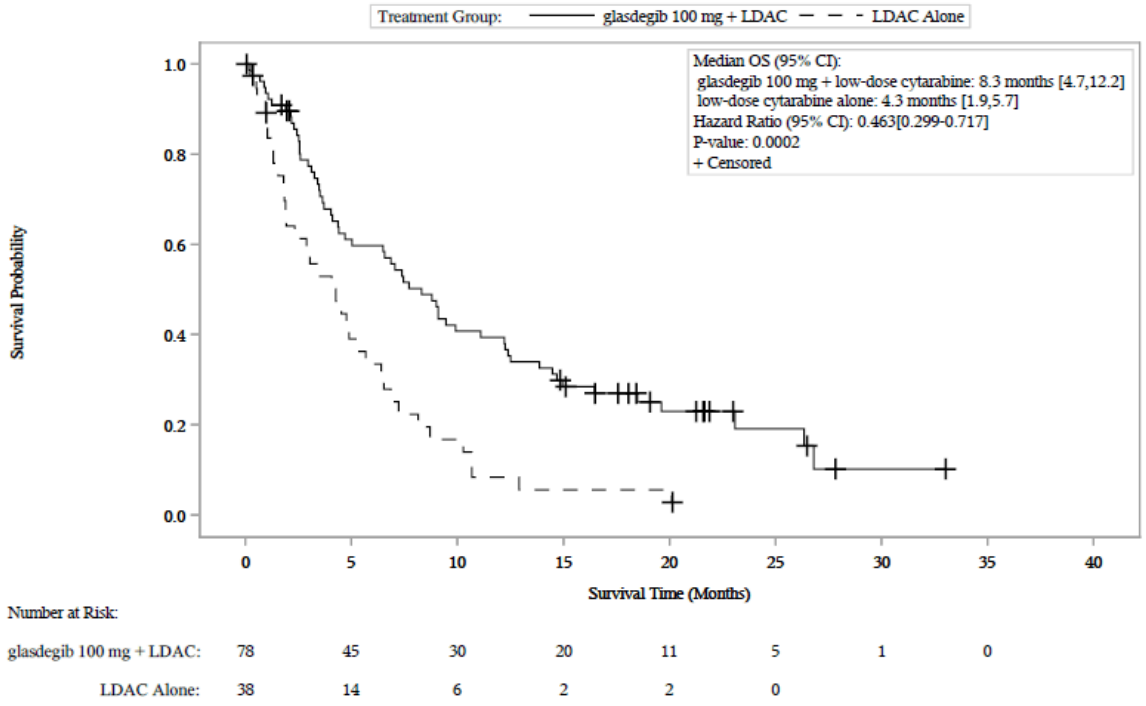
Endpoint/Study Population	DAURISMO With Low-Dose Cytarabine	Low-Dose Cytarabine Alone
OS	N=78	N=38
Median survival, months (95% CI)	8.3 (4.7, 12.2)	4.3 (1.9, 5.7)
Hazard ratio (95% CI)[a]	0.46 (0.30, 0.72)	
p-value[b]	0.0002	
CR	N=14	N=1
CR rate (in %, 95% CI)	17.9 (9.4, 26.5)	2.6 (0.0, 7.7)

Abbreviations: AML = acute myeloid leukemia; N = number of patients; OS = overall survival; CI = confidence interval; CR = complete response.

[a.] Hazard ratio (DAURISMO with low-dose cytarabine/low-dose cytarabine alone) based on the Cox Proportional hazards model stratified by cytogenetic risk.

[b.] 1-sided p-value from log-rank test stratified by cytogenetic risk.

Figure 1 - Study B1371003 - Kaplan-Meier Plot of Overall Survival for Patients with AML



Abbreviations: CI = confidence interval; OS = overall survival; LDAC = low-dose cytarabine.

16 NON-CLINICAL TOXICOLOGY

Repeat-Dose Toxicity: The primary target organ findings following repeat oral administration of glasdegib in rats and dogs for up to 26 and 39 weeks in duration, respectively, included the kidney (degeneration/necrosis) in rat and dog, the liver (necrosis/inflammation) in dog only, and the testis (degeneration), growing incisor teeth (necrosis/broken), growing bone (partial to full closure of epiphysis), and peripheral nerve (axonal degeneration) in rat only. Additional clinical observations of

weight loss, alopecia and muscle tremors/twitching, known class effects of SMO inhibitors, were observed in both species. These systemic toxicities were generally dose-dependent and observed at exposures ranging from approximately <0.03 to 8 times the clinically relevant exposure based on nonclinical to clinical comparison of the observed unbound AUC at the recommended clinical dose of 100 mg once daily.

Complete reversibility of toxicities to the kidney (degeneration/necrosis), peripheral nerve (axonal degeneration), seminiferous tubule (testicular degeneration), and the clinical observations of muscle tremors/twitching was demonstrated following up to 16-week recovery, whereas partial recovery was demonstrated in the liver (necrosis/inflammation). The observations of weight loss, of alopecia, bone and teeth effects, and testicular hypospermatogenesis did not recover. In addition, QTc prolongation was identified in telemetered dogs at unbound C_{max} exposures approximately 4-times the observed unbound C_{max} exposure at the recommended clinical dose of 100 mg once daily.

Carcinogenicity: Carcinogenicity studies have not been conducted with glasdegib.

Genotoxicity: Glasdegib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro chromosome aberration assay in human lymphocytes. Glasdegib was not clastogenic or aneugenic in the rat micronucleus assay.

Reproductive Toxicity: Effects on male reproductive organs were observed in animals at 50 mg/kg/day (approximately 8 times the unbound human clinical exposure based on AUC). Safety margin for NOAEL (10 mg/kg/day) is 0.6, hence lower than clinically relevant.

The effect of testicular degeneration did recover whereas the hypospermatogenesis did not recover.

Developmental Toxicity: In embryo-fetal developmental toxicity studies, repeat dosing of glasdegib to pregnant rats and rabbits during the period of organogenesis resulted in embryotoxicity, fetotoxicity, and teratogenicity. Glasdegib administration resulted in complete resorption of fetuses and/or low fetal body weights, and fetal developmental abnormalities and malformations (craniofacial malformations, malformed limbs, paws/digits, trunk and tail, dilation of brain, malpositioned/ malformed eyes, misshapen head, small tongue, absent palate, teeth and viscera, diaphragmatic hernia, edema, heart defects, rib and vertebral abnormalities, malformed or absent structures in the appendicular skeleton (notably the long bones)). Embryo-fetal lethality (88% resorption in rats and 100% resorption in rabbit) was observed at maternal systemic exposure multiples of approximately 4-times and 3-times the unbound human AUC in rats and rabbits, respectively. Severe developmental malformations were observed at maternal systemic C_{max} and AUC exposures in rats and rabbits approximately 0.71 times and 0.6 times, respectively to the relevant human exposure at the recommended dose of 100 mg once daily.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]DAURISMO®

Glasdegib Tablets

Read this carefully before you start taking **DAURISMO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DAURISMO**.

Your acute myeloid leukemia (AML) will be treated with **DAURISMO** in combination with another drug called cytarabine. Read the Patient Information leaflets for the other drug as well as this one.

Serious Warnings and Precautions

Only take DAURISMO under the care of a doctor who knows how to use anti-cancer drugs. They should have a full understanding of the risks and monitoring needs of DAURISMO.

- DAURISMO can cause your baby to die before it is born or cause your baby to have severe birth defects.
- DAURISMO is available only through a controlled distribution program called the DAURISMO Pregnancy Prevention Program (DPPP).
- DAURISMO is not for children or adolescents less than 18 years old.
- DAURISMO may harm fertility in males and females.

For female patients:

- Do not use DAURISMO if you are pregnant.
- If you are able to become pregnant, your healthcare professional will do a pregnancy test within 7 days before you start taking DAURISMO, and every month during treatment.
- If you are able to become pregnant, use two highly effective birth control methods while taking DAURISMO (including dose interruptions) and for at least 30 days after your last dose.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant while taking DAURISMO.

For male patients:

- It is not known if DAURISMO passes into semen. Sexual partners might be at risk of exposure through semen.
- Do not donate semen while taking DAURISMO and for at least 30 days after your last dose.
- Use a condom that has a sperm killing substance (spermicide) when having sexual intercourse with a woman (even if she is pregnant). The condom must be used:
  - while taking DAURISMO (including dose interruptions), and
  - for 30 days after your last dose of DAURISMO, and
  - even if you had a vasectomy.
- If your female partner is able to become pregnant, she must also use a highly effective method of birth control, while you are taking DAURISMO (including dose interruptions) and for at least 30 days after your last dose.

What is DAURISMO used for?

DAURISMO is used to treat acute myeloid leukemia (AML) that has not been treated before. It is used together with a cancer drug called cytarabine, and they are only used in adults who:

- are 75 years of age or older
  or
- cannot receive intensive chemotherapy.

DAURISMO can only be given to patients who are registered in and meet all conditions of the DAURISMO Pregnancy Prevention Program (DPPP), which is a controlled distribution program for DAURISMO.

How does DAURISMO work?

Glasdegib, the medicinal ingredient in DAURISMO, is a type of drug called a hedgehog pathway inhibitor. It works by stopping cancer cells from dividing and growing.

What are the ingredients in DAURISMO?

Medicinal ingredients: glasdegib (as glasdegib maleate)

Non-medicinal ingredients: dibasic calcium phosphate anhydrous, hypromellose, iron oxide yellow (25 mg tablet), iron oxide red and iron oxide yellow (100 mg tablet), lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate; titanium dioxide, triacetin

DAURISMO comes in the following dosage forms:

Tablets, 25 mg, 100 mg

Do not use DAURISMO if:

- you are pregnant or plan to become pregnant.
- you are female that can get pregnant but cannot or are unwilling to use effective birth control.
- you are breastfeeding or plan to breastfeed.
- you are male but cannot or are unwilling to use effective birth control.
- you are allergic to any ingredients in this drug or the container.
- you are a child or adolescent less than 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DAURISMO. Talk about any health conditions or problems you may have, including if you:

- Have heart rhythm problems, including:
  - Long QT interval syndrome (changes in the electrical system of your heart).
  - Heart arrhythmias. This is when heartbeats are not normal and can cause:
    - heart fibrillation (heart shakes instead of pumping blood).
    - heart tachycardia (heart beats faster than normal when resting).
- Have blood salt (electrolyte) levels that are not normal.
- Have liver or kidney problems.

Other warnings you should know about:

- Do not donate blood or blood products while taking DAURISMO and for at least 30 days after your last dose. Your blood might be given to a female that can get pregnant.
- DAURISMO may harm fertility in males and females. It may affect the ability for males to father children, and for females to have children. Talk to your healthcare professional about ways to keep your fertility before you start treatment.

Female Patients: Important Warnings

- Do not take DAURISMO if you are pregnant or if you are still able to get pregnant and are not using highly effective birth control.
- You must avoid becoming pregnant while you are taking DAURISMO and for at least 30 days after your last dose.
- Your healthcare professional will talk to you about the possible serious risks of DAURISMO to your unborn baby if you become pregnant.
- DAURISMO can cause your baby to die before it is born or cause your baby to have severe birth defects.
- If you can get pregnant, your healthcare professional will do a pregnancy test:
  - within 7 days before you start treatment with DAURISMO, and
  - every month during treatment with DAURISMO.
- You will continue to have pregnancy tests, even if you stop menstruating, during treatment.
- You will not be given DAURISMO if you are pregnant.
- Your healthcare professional will talk to you about what birth control methods are right for you.
- Unless you commit to not having sexual intercourse, you must use two highly effective birth control methods while taking DAURISMO and for at least 30 days after your last dose.
- Talk to your healthcare professional if you committed to not having sexual intercourse but you have changed your mind. You must commit to using two highly effective birth control methods.
- You must use two highly effective birth control methods even if:
  - you have a history of infertility, your periods have stopped, are irregular, or have abnormal menstrual bleeding.
- If you become pregnant or think you are pregnant during treatment with DAURISMO, stop taking DAURISMO and tell your healthcare professional right away. They will explain the risks to you.
- Do not breastfeed during treatment with DAURISMO and for at least 30 days after the final dose. Talk to your healthcare professional about the best way to feed your baby during this time. It is not known if DAURISMO passes into breast milk.

Male Patients: Important Warnings

- You must tell your female partner:
  - that you are taking DAURISMO, and
  - the possible serious risks to an unborn baby if she becomes pregnant by you. This could happen during your treatment of DAURISMO (including dose interruptions) or at least 30 days after your last dose.
- Use a condom that has a sperm killing substance (spermicide) when having sexual intercourse with a woman (even if she is pregnant). The condom must be used:
  - while taking DAURISMO (including dose interruptions), and

    - for 30 days after your last dose of DAURISMO, and
    - even if you had a vasectomy.
- If your female partner is able to become pregnant, she must also use a highly effective method of birth control while you are taking DAURISMO (including dose interruptions) and for at least 30 days after your last dose.
- Do not donate semen while taking DAURISMO (including dose interruptions) and for at least 30 days after your last dose.
- Tell your healthcare professional right away if your female partner is or maybe pregnant.

Driving and Using Machines: DAURISMO can cause fatigue. Before you do tasks which may require attention, wait until you know how you respond to DAURISMO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

DAURISMO and certain other drugs can cause heart rhythm problems. Avoid taking these other drugs with DAURISMO. Taking these drugs together with DAURISMO might make your heath rhythm problems worse. Your healthcare professional will determine if other treatments can be used.

The following may interact with DAURISMO:

- Nafcillin, rifampin, and troleandomycin, used to treat bacterial infections (antibiotics)
- Ketoconazole, itraconazole, posaconazole and voriconazole, used to treat fungal infections.
- Ritonavir, indinavir, lopinavir, efavirenz, etravirine, elvitegravir, cobicistat and tipranavir, used to treat HIV.
- Boceprevir, telaprevir, paritaprevir, ombitasvir, dasabuvir and danoprevir, used to treat viral infections like hepatitis C.
- Conivaptan, used to treat blood salt levels.
- Carbamazepine and phenytoin, used to treat epilepsy.
- St. John's Wort, used to treat depression.
- Enzalutamide and mitotane, used to treat cancers.
- Bosentan, used to treat high blood pressure in lung blood vessels.
- Modafinil, used to treat sleepiness.

Ask your healthcare professional if you are not sure whether a drug you are taking is listed. Tell them if you are prescribed any new drugs.

How to take DAURISMO:

- Take DAURISMO as your healthcare professional tells you. It is taken with another drug for acute myeloid leukemia (AML).
- Your health care professional will tell you how much, when, and how you will take the other drug.
- Treatment may continue until the cancer gets worse or you get side effects that could prevent treatment continuation.
- Take DAURISMO once a day, at about the same time each day.
- Take DAURISMO with or without food.
- If you vomit after taking a dose of DAURISMO, do not take another dose on that day. Take your next dose at your regular time.

- Do not take more than the recommended dose prescribed by your healthcare professional.
- Do not change the DAURISMO dose or schedule unless your healthcare professional tells you to.

Usual dose:

Adults:

- Take 100 mg of DAURISMO once daily, by mouth, with another drug for acute myeloid leukemia (AML).
- Your healthcare professional will monitor your health. They may interrupt, reduce, or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much [Brand name], contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of DAURISMO is missed:

- If you are less than 12 hours late, take the missed dose as soon as you remember. Take the next dose at your regular time.
- If you are more than 12 hours late, skip the dose for that day. Wait until the regular time for your next dose.
- Do not take two doses within 12 hours to make up for a missed dose.

What are possible side effects from using DAURISMO?

These are not all the possible side effects you may have when taking DAURISMO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- feeling tired, weak
- headache
- pain: muscle, limb, joints, bones, stomach, back
- muscle spasms and tightness
- nausea (feeling sick)
- swelling of arms, legs, face
- decreased appetite
- change in taste
- loose tooth, tooth ache
- pain or sores in your mouth or throat
- constipation
- hair loss
- weight loss

DAURISMO can cause heart electrical signal changes and abnormal blood and urine test results. Your healthcare professional will do some tests before, during and after your treatment. These include checking your heart rhythm and blood cell count, salt and enzyme levels. More frequent tests might be needed. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Eye hemorrhage (eye bleeding): blurred vision, pain when exposed to bright light, a layer of blood may be visible on white part of eye, eye bruising			X
Gastrointestinal (GI) bleeding (bleeding anywhere along the GI tract between mouth and anus): (bleeding in esophagus, stomach or first part of small intestines): blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness; (bleeding from large intestine, rectum): bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			X
Hematuria (blood in the urine): pink, red or very dark urine			X
Hemoptysis: coughing up blood			X
Intracerebral hemorrhage (bleeding in the brain): sudden, severe headache; confusion; nausea and vomiting; seizures; loss of consciousness			X
Pneumonia (infection in the lungs): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Purpura (bleeding under the skin): bruising, purple spotted spots or rash, discoloration of skin	X		
Febrile neutropenia: infections, fatigue, fever, aches, pains and flu-like symptoms		X	
COMMON			
Acute respiratory failure: blue color on skin, lips, and fingernails; feel sleepy; irregular heartbeats; loss of consciousness; sudden worsening of shortness of breath			X
Acute kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain.			X
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		X	
Cardiac arrhythmias (abnormal heart rhythms): irregular pulse, slow pulse, rapid pulse, palpitations, shortness of breath, dizziness			X
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		X	
Mucositis (inflammation and ulceration of the mucous membranes lining the digestive tract): painful, red, shiny or swollen gums, tongue, mouth or throat sores, blood in the mouth, difficult or painful swallowing or talking, dry mouth, mild burning, or pain when eating food		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			X
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		X	
Prolongation of QT interval (a heart rhythm condition): Irregular heartbeat, fainting, loss of consciousness, seizures, dizziness, lightheaded			X
Sepsis and septic shock (Infection of the blood): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat.		X	
Skin disorders: Rash, painful red lumps, pain in joints and muscles	X		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store DAURISMO at 15°C to 30°C.

Keep DAURISMO and all medicines out of reach and sight of children.

If you want more information about DAURISMO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

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