SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Daurismo 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains glasdegib maleate equivalent to 100 mg of glasdegib.

Excipient with known effect
Each film-coated tablet contains 5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

11 mm round, pale orange film-coated tablet debossed with “Pfizer” on one side and “GLS 100” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.

4.2 Posology and method of administration

Daurismo should only be prescribed by or under the supervision of a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose is 100 mg glasdegib once daily in combination with low-dose cytarabine (see section 5.1). Glasdegib should be continued as long as the patient is deriving clinical benefit.

Delayed or missed doses of glasdegib
If a dose is vomited, a replacement dose should not be administered; patients should wait until the next scheduled dose is due. If a dose is missed or not taken at the usual time, then it should be taken as soon as the patient remembers unless more than 10 hours have passed since the scheduled dosing time, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

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

Dose modification and management guidelines for specific adverse reactions are provided in Tables 1, 2, 3 and 4.

No starting dose adjustments are required on the basis of patient age, race, gender, or body weight (see section 5.2).

Assessment of laboratory values and QT abnormalities prior to treatment initiation
Complete blood counts, electrolytes, renal, and hepatic function should be assessed prior to the initiation of treatment and at least once weekly for the first month (see section 4.4). Serum creatinine kinase (CK) levels should be obtained prior to initiating therapy and as indicated clinically thereafter (e.g. if muscle signs and symptoms are reported; see section 4.4). Electrocardiograms (ECGs) should be monitored prior to the initiation of treatment, approximately one week after initiation, and then once monthly for the next two months to assess for QT corrected for heart rate (QTc) prolongation (see section 4.4).

Table 1. Dose modification and management for adverse reactions – QT interval prolongation
(corrected QT interval prolongation on at least 2 separate electrocardiograms (ECGs))

Adverse reaction: ECG QT Prolonged	**Dose modification and management recommendations**
Corrected QT interval 480 msec to 500 msec	Assess electrolyte levels and supplement as clinically indicated. Review and adjust concomitant medicinal products with known QT prolonging effects (see section 4.5). Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation to less than or equal to 480 msec.
Corrected QT interval greater than 500 msec	Assess electrolyte levels and supplement as clinically indicated. Review and adjust concomitant medicinal products with known QT prolonging effects (see section 4.5).

	Interrupt Daurismo. Resume Daurismo at a reduced dose of 50 mg once daily when corrected QT interval returns to within 30 msec of baseline or less than or equal to 480 msec. Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation. Consider re-escalating the dose of Daurismo to 100 mg daily if an alternative aetiology for the QT prolongation can be identified.
Corrected QT interval prolongation and life-threatening arrhythmia	Discontinue Daurismo permanently.

Table 2. Dose modification and management for CK elevations and muscle-related adverse events

Adverse reaction: Severity of CK elevation	**Dose modification and management recommendations**
Grade 1 [CK elevation > ULN - 2.5 x ULN]	Continue Daurismo at the same dose 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 measure CK monthly thereafter. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. If symptoms re-occur, interrupt Daurismo until resolution to baseline. Re-introduce Daurismo at 50 mg daily and follow the same monitoring 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 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 return to baseline, consider resuming Daurismo at 50 mg daily and measure CK levels weekly for 2 months and monthly thereafter; otherwise discontinue treatment permanently.

Abbreviations: CK=creatine kinase; Cr=creatinine; ULN=upper limit of normal; CTCAE=Common Terminology Criteria for Adverse Events.

Table 3. Dose modification and management for adverse reactions – Haematologic toxicity

Adverse reaction: Haematologic toxicity	**Dose modification and management recommendations**
Platelets less than 10 x 10^9/L for more than 42 days in the absence of disease	Discontinue Daurismo and low-dose cytarabine permanently.
Neutrophil count less than 0.5 x 10^9/L for more than 42 days in the absence of disease	Discontinue Daurismo and low-dose cytarabine permanently.

Table 4. Dose modification and management for adverse reactions – Nonhaematologic toxicity

Adverse reaction: Nonhaematologic toxicity	**Dose modification and management recommendations** If adverse reaction is attributed to low-dose cytarabine and not to Daurismo, low-dose cytarabine may be modified while Daurismo dosing should be continued.
Grade 3*	Interrupt Daurismo and/or low-dose cytarabine until symptoms improve to Grade ≤ 1 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/or low-dose cytarabine.†
Grade 4*	Withhold Daurismo until symptoms improve 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.
† If a decision is made to permanently discontinue low-dose cytarabine, Daurismo should also be discontinued, unless the individual patient is deriving clinical benefit and is tolerating treatment with Daurismo.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events.

Dose modification for concomitant use with moderate CYP3A4 inducers
Concomitant use of Daurismo with moderate CYP3A4 inducers should be avoided. If concomitant use of moderate CYP3A4 inducers cannot be avoided, the dose of Daurismo should be increased as tolerated as shown in Table 5. After the moderate CYP3A4 inducer has been discontinued for 7 days, the Daurismo dose taken prior to initiating the moderate CYP3A4 inducer should be resumed (see section 4.5).

Table 5. 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

Special populations

Hepatic impairment
No dose adjustments are recommended in patients with mild, moderate, or severe hepatic impairment (see section 5.2).

Renal impairment
No dose adjustments are recommended for patients with mild, moderate, or severe renal impairment. No data are available in patients requiring haemodialysis (see section 5.2).

Elderly (≥ 65 years of age)
No dose adjustment in elderly patients is required (see section 5.2).

Paediatric population
The safety and efficacy of Daurismo in the paediatric population (< 18 years of age) have not been established. Daurismo should not be used in the paediatric population because there is no expected significant therapeutic benefit over existing treatments for paediatric patients (see section 5.1).

Method of administration

Daurismo is for oral use. It may be taken with or without food.

Patients should be encouraged to take their dose at approximately the same time each day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Embryo-foetal toxicity

Based on its mechanism of action and findings from animal embryo-foetal developmental toxicity studies, Daurismo can cause embryo-foetal death or severe

birth defects when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus (see section 4.6).

Daurismo should not be used during pregnancy and in women of childbearing potential not using contraception. The pregnancy status of female patients of childbearing potential should be verified prior to initiating treatment with Daurismo. Women of childbearing potential should be advised to always use effective contraception during treatment with Daurismo and for at least 30 days after the last dose (see section 4.6).

Males
Glasdegib may be present in semen. Male patients with female partners should be advised of the potential risk of exposure through semen and to always use effective contraception, including a condom (with spermicide, if available), even after vasectomy, to avoid exposure of a pregnant partner or a female partner of childbearing potential during treatment with Daurismo and for at least 30 days after the last dose (see section 4.6).

If a female patient or female partner of a male patient becomes pregnant, or suspects a pregnancy during treatment with Daurismo or during the 30 days after the last dose, they must inform their healthcare provider immediately (see section 4.6).

Based on non-clinical safety findings, glasdegib has the potential to impair reproductive function in males. Men should seek advice on effective fertility preservation prior to initiating treatment with Daurismo (see section 4.6).

QT interval prolongation

In a randomised study (Study 1) of patients with AML and high-risk MDS (myelodysplastic syndrome) treated with Daurismo with low-dose cytarabine vs low-dose cytarabine alone, Grade 3/4 ECG QT prolonged was reported in 3.5% of patients treated with Daurismo with low-dose cytarabine compared to 2.4% of the patients treated with low-dose cytarabine alone.

Electrolytes should be assessed prior to initiation of Daurismo, at least once weekly for the first month, and then once monthly for the duration of therapy. Electrolyte abnormalities should be corrected.

Concomitant medicinal products should be assessed. For medicinal products that have known QT prolonging effects and/or strong CYP3A4 inhibitor potential, alternatives should be considered.

ECGs should be monitored 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. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products with known QT prolonging effects, more frequent ECG monitoring is recommended. ECG should be repeated if abnormal. Abnormalities should be managed promptly, and dose modifications should be considered (see sections 4.2 and 4.5).

Blood cell counts and hepatic function monitoring

Complete blood counts and hepatic function should be assessed prior to the initiation of therapy and at least once weekly for the first month. Thereafter, hepatic function and blood cell counts should be monitored as clinically indicated but at least monthly. In the event of hepatic or haematologic toxicity, dose modifications may be needed (see section 4.2).

Muscle-related adverse events

In Study 1, muscle spasms were observed in 22.6% of patients treated with Daurismo with low-dose cytarabine compared to 4.8% of the patients treated with low-dose cytarabine alone.

All patients starting therapy with Daurismo must be informed of the risk of muscle-related adverse events. They must be instructed to report promptly any unexplained muscle pain, tenderness or weakness occurring during treatment with Daurismo or if symptoms persist after discontinuing treatment.

Serum CK levels should be obtained prior to initiating Daurismo and as clinically indicated thereafter (e.g. if muscle signs and symptoms are reported). Management of high-grade CK elevation based on current standards of medical practice and following appropriate treatment guidelines is recommended. Dose modification or management recommendations should be followed (see section 4.2).

Renal impairment

Patients with pre-existing renal impairment or risk factors for renal dysfunction should be monitored closely. Renal function should be assessed prior to initiation of therapy and at least once weekly for the first month of therapy with Daurismo. Electrolytes and renal function should be monitored once monthly for the duration of therapy (see section 4.2).

Excipients

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of glasdegib

In vitro, CYP3A4 is responsible for the majority of glasdegib depletion and contributed to the formation of other minor oxidative metabolites, with CYP2C8 and UGT1A9 playing a minor role in the metabolism of glasdegib.

Substances that may increase glasdegib plasma concentration
CYP3A4 inhibitors
Ketoconazole, a strong inhibitor of CYP3A4, dosed at 400 mg once daily for 7 days, increased the mean area under the curve (AUC_{inf}) by ~2.4-fold and maximum plasma concentration (C_{max}) by 40% of a single 200 mg oral dose of glasdegib in healthy

subjects. Caution should be used when administering concomitantly with strong CYP3A4 inhibitors (e.g. boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, grapefruit or grapefruit juice) as an increase in glasdegib plasma concentration may occur. If possible, alternate concomitant medicinal product with no or minimal CYP3A4 inhibition potential is recommended (see section 4.4).

Gastric pH altering medicinal products
Coadministration of a single 100 mg glasdegib dose under fasted condition with multiple doses of the proton-pump inhibitor (PPI), rabeprazole, resulted in no change in glasdegib plasma exposure (AUC_{inf} ratio: 100.6%). Concomitant administration of glasdegib with acid-reducing agents (including PPIs, H_2-receptor antagonists, and locally acting antacids) is permitted.

Substances that may decrease glasdegib plasma concentration
CYP3A4 inducers
Rifampicin, a strong inducer of CYP3A4, administered at a dose of 600 mg once daily for 11 days, reduced the mean AUC_{inf} by 70% and C_{max} by 35% of a single 100 mg dose of glasdegib in healthy subjects. Concomitant use with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's Wort) should be avoided, as this is likely to decrease glasdegib plasma concentrations.

Simulations using physiologic-based pharmacokinetic modelling suggested that coadministration of efavirenz (a moderate inducer of CYP3A4) with glasdegib decreased glasdegib AUC_{inf} by 55% and C_{max} by 25%. Concomitant use of moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided as they may also reduce glasdegib plasma concentrations (see section 4.4). If concomitant use of moderate CYP3A4 inducers cannot be avoided, the dose of Daurismo should be increased (see section 4.2).

Effect of glasdegib on the pharmacokinetics of other medicinal products

Pharmacodynamic interactions
Medicinal products known to prolong QT interval
Glasdegib may prolong QT interval. Therefore, the concomitant use of glasdegib with other medicinal products known to prolong QT interval or induce Torsades de Pointes (such as amiodarone, disopyramide, dofetilide, ibutilide, sotalol, quinidine, droperidol, haloperidol, methadone, moxifloxacin, pimozide) should be carefully considered (see sections 4.2 and 4.4).

Pharmacokinetic interactions

Drug transporters
In vitro studies indicated that glasdegib may have the potential to inhibit P-glycoprotein (P-gp, gastrointestinal [GI] tract) and breast cancer resistance protein (BCRP, systemically and at the GI tract) mediated transport at clinically relevant concentrations. Therefore, narrow therapeutic index substrates of P-gp (e.g. digoxin) or BCRP should be used with caution in combination with glasdegib.

In vitro studies of transporter inhibition
In vitro studies indicated that glasdegib may have the potential to inhibit (MATE)1 and MATE2K at clinically relevant concentrations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
If Daurismo is used in women of childbearing potential, they should be advised to avoid becoming pregnant. The pregnancy status of female patients of childbearing potential should be verified prior to initiating treatment. If the patient becomes pregnant while taking Daurismo, the patient should be apprised of the potential hazard to the foetus.

Based on its mechanism of action and findings from animal embryo-foetal developmental studies, Daurismo can cause foetal harm when administered to a pregnant woman. Women of childbearing potential who are receiving this medicinal product should always use effective contraception during treatment with Daurismo and for at least 30 days after the last dose. If a female patient becomes pregnant, or suspects a pregnancy, during treatment with Daurismo or during the 30 days after the last dose, she must notify her healthcare provider immediately (see section 4.4).

Males
Glasdegib may be present in semen. Male patients should not donate semen during treatment with Daurismo and for at least 30 days after the last dose. Male patients with female partners should be advised of the potential risk of exposure through semen and to always use effective contraception, including a condom (with spermicide, if available), even after a vasectomy, to avoid exposure of a pregnant partner or a female partner of childbearing potential during treatment with Daurismo and for at least 30 days after the last dose. Male patients must inform their healthcare provider immediately if their female partner becomes pregnant during treatment with Daurismo or during the 30 days after the last dose (see section 4.4).

Pregnancy
There are no data on the use of Daurismo in pregnant women. Based on its mechanism of action and findings in animal embryo-foetal developmental toxicity studies, glasdegib can cause foetal harm when administered to a pregnant woman (see section 5.3). Daurismo should not be used during pregnancy and in women of childbearing potential not using contraception (see section 4.4).

Breast-feeding
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 breast-fed child. It is unknown whether glasdegib and its metabolites are excreted in human milk. Given the potential for serious adverse reactions in breast-feeding children from glasdegib, breast-feeding is not recommended during treatment with Daurismo and for at least one week after the last dose (see section 5.3).

Fertility
Based on non-clinical safety findings, glasdegib has the potential to impair reproductive function in males. Men should seek advice on effective fertility

preservation prior to initiating treatment with Daurismo. Based on its mechanism of action, Daurismo may impair female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Daurismo has minor influence on the ability to drive and use machines. However, patients experiencing fatigue or other symptoms (e.g., muscle cramps, pain, nausea) affecting the ability to react normally while taking Daurismo should exercise caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Daurismo is based on data from clinical studies, including Study 1 in 84 patients with AML (N=75) and high-risk MDS (N=9). The median exposure to Daurismo across the dataset was 75.5 days.

The most frequently (≥ 20%) reported adverse reactions in patients receiving Daurismo were anaemia (45.2%), haemorrhages (45.2%), febrile neutropenia (35.7%), nausea (35.7%), decreased appetite (33.3%), fatigue (30.9%), muscle spasms (30.9%), thrombocytopenia (30.9%), pyrexia (29.7%), diarrhoea (28.5%), pneumonia (28.5%), dysgeusia (26.1%), oedema peripheral (26.1%), constipation (25%), abdominal pain (25%), rash (25%), dyspnoea (25%), vomiting (21.4%), and weight decreased (20.2%).

The most frequently reported adverse reactions leading to dose reductions in patients receiving Daurismo were muscle spasms (4.7%), fatigue (3.5%), febrile neutropenia (3.5%), anaemia (2.3%), thrombocytopenia (2.3%), and electrocardiogram QT prolonged (2.3%). The most frequently reported adverse reactions leading to permanent discontinuation in patients receiving Daurismo were pneumonia (5.9%), febrile neutropenia (3.5%), and nausea (2.3%).

Tabulated list of adverse reactions

Table 6 presents adverse reactions reported with Daurismo. The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in decreasing order of all grade frequencies.

Table 6: Adverse reactions reported in clinical studies (N=84)

		All grades
System organ class	**Preferred term**	

		Frequency	All grades (%)	Grade ≥ 3 (%)
Infections and infestations	Pneumonia	Very common	28.5	23.8
	Sepsis	Common	5.9	5.9
	Urinary tract infection	Common	5.9	1.1
Blood and lymphatic system disorders	Anaemia	Very common	45.2	41.6
	Febrile neutropenia	Very common	35.7	35.7
	Thrombocytopenia	Very common	30.9	30.9
	Neutropenia	Very common	15.4	11.9
Metabolism and nutrition disorders	Decreased appetite	Very common	33.3	3.5
Nervous system disorders	Dysgeusia[a]	Very common	26.1	0
Cardiac disorders	Electrocardiogram QT prolonged[b]	Common	8.3	3.5
	Atrial fibrillation	Common	7.1	2.3
Vascular disorders	Haemorrhages[c]	Very common	45.2	11.9
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	25	7.1
Gastrointestinal disorders	Nausea	Very common	35.7	2.3
	Diarrhoea	Very common	28.5	4.7
	Constipation	Very common	25	1.1
	Abdominal pain[d]	Very common	25	0
	Vomiting	Very common	21.4	2.3
	Stomatitis	Common	4.7	0
Skin and subcutaneous tissue disorders	Rash[e]	Very common	25	2.3
	Alopecia	Very common	10.7	0
Musculoskeletal and connective tissue disorders	Muscle spasms[f]	Very common	30.9	5.9
	Arthralgia	Very common	11.9	0
General disorders and administration site conditions	Fatigue	Very common	30.9	14.2
	Weight decreased	Very common	20.2	2.3
	Pyrexia	Very common	29.7	2.3
	Oedema peripheral	Very common	26.1	0
Investigations	Platelet count decreased	Very common	16.6	16.6
	White blood cell count decreased	Very common	15.4	13
	Neutrophil count decreased	Very common	13	13

[a.] Dysgeusia includes the following preferred terms: dysgeusia, ageusia.

[b.] Electrocardiogram QT prolonged includes the following preferred terms: electrocardiogram QT prolonged, ventricular tachycardia.

[c.] Haemorrhages includes the following preferred terms: petechiae, epistaxis, contusion, haematoma, haemorrhage intracranial, purpura, rectal haemorrhage, anal haemorrhage, ecchymosis, gastrointestinal haemorrhage, gingival bleeding, haematuria, haemorrhage, mouth haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, eye contusion, eye haemorrhage, gastric haemorrhage, haematemesis, haemoptysis, haemorrhoidal haemorrhage, implant site haematoma, injection site bruising, retroperitoneal haematoma, subarachnoid haemorrhage, thrombotic thrombocytopenic purpura, tracheal haemorrhage, urethral haemorrhage.

[d.] Abdominal pain includes the following preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower.
[e.] Rash includes the following preferred terms: erythema, pruritus, rash, rash macular, rash maculo-papular, rash pruritic.
[f.] Muscle spasms includes the following preferred terms: muscle contractions involuntary, muscle spasms, muscle tightness, musculoskeletal pain, myalgia.

Description of selected adverse reactions

Muscle spasms
In Study 1, muscle spasms (all grades) were reported in 22.6% of patients in the Daurismo with low-dose cytarabine arm compared to 4.8% in the low-dose cytarabine alone arm. Grades 3 and 4 muscle spasms were reported in 4.7% of patients in the Daurismo with low-dose cytarabine arm compared to none in the low-dose cytarabine alone arm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific antidote for Daurismo. Management of Daurismo overdose should consist of symptomatic treatment and ECG monitoring.

Glasdegib has been administered in clinical studies up to a dose of 640 mg/day. The dose-limiting toxicities reported were nausea, vomiting, dehydration, hypotension, fatigue, dizziness, hypoxia, pleural effusion and peripheral oedema.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XJ03

Mechanism of action

Glasdegib is an inhibitor of the Hedgehog (Hh) signal transduction pathway that binds to Smoothened (SMO), a transmembrane protein, leading to decreased Glioma-

Associated Oncogene (GLI) transcription factor activity and downstream pathway signalling. Hh pathway signalling is required for maintaining a leukaemic stem cell (LSC) population thus, glasdegib binding to and inhibiting SMO reduces GLI1 levels in AML cells and the leukaemic initiating potential of AML cells. Hh pathway signalling is also implicated in resistance to chemotherapy and targeted therapy. In a preclinical model of AML, glasdegib in combination with low-dose cytarabine inhibited increases in tumour size to a greater extent than glasdegib or low-dose cytarabine alone. However, mechanism of action of the combination is not fully understood.

Cardiac electrophysiology

Heart rate corrected QT (QTc) interval prolongation has been observed in patients treated with Daurismo at a supratherapeutic dose of > 270 mg. The effect of glasdegib administration on corrected QT interval was evaluated in a randomised, 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 corrected QT interval change was 8.03 msec (90% CI: 5.85, 10.22 msec). At approximately twice the therapeutic concentration (supratherapeutic, 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. None of the subjects met categorical criterion of absolute corrected QT interval of ≥ 480 msec or increase from baseline in corrected QT interval ≥ 30 msec after receiving any treatment. None of the ECG abnormalities were considered clinically significant or reported as adverse events by the investigator (see section 4.4).

Additionally, serial, triplicate ECGs were collected following a single and multiple dosing to evaluate the effect of single agent glasdegib on the corrected QT interval in 70 patients with advanced cancer (5 mg to 640 mg once daily). Based on the exposure-response analysis, the estimated mean change from baseline in QTc was 5.30 msec (95% CI: 4.40, 6.24 msec) at the mean observed C_{max} at steady state following administration at the recommended 100 mg once daily dose of glasdegib.

Clinical efficacy and safety

Daurismo in combination with low-dose cytarabine was investigated in a multicentre, randomised, open-label Phase 2 study (Study 1) in a total of 132 patients, which included 116 patients with previously untreated *de novo* or secondary AML who were not eligible to receive intensive chemotherapy as defined by meeting 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 randomised 2:1 to receive Daurismo (100 mg orally once daily) with low-dose cytarabine (20 mg SC twice daily on days 1 to 10 of the 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 at randomisation by prognostic risk factor (good/intermediate or poor) based on cytogenetics.

The baseline demographic and disease characteristics are shown in Table 7. The two treatment arms were generally balanced with respect to the baseline demographics and disease characteristics. Across both arms, 40% of the AML patients had poor cytogenetic risk and 60% had good/intermediate cytogenetic risk.

Efficacy was established by an improvement in overall survival (OS defined from the date of randomisation to death of any cause) in the Daurismo with low-dose

cytarabine arm, compared to low-dose cytarabine alone. After a median follow-up of approximately 20 months with 81% deaths observed, the Daurismo with low-dose cytarabine arm was superior to low-dose cytarabine alone in AML patients (Figure 1). The efficacy results are shown in Table 8.

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 (76)	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 characteristics		
Disease history, N (%)		
De Novo AML	38 (49)	18 (47)
Secondary AML	40 (51)	20 (53)
Prior hypomethylating agent (decitabine or azacitidine) use, N (%)	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, N (%)	52 (67)	20 (53)
Baseline serum creatinine > 1.3 mg/dL, N (%)	15 (19)	5 (13)

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

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

Table 8. AML efficacy results from Study 1

Endpoint/study population	Daurismo with low-dose cytarabine	Low-dose cytarabine alone
OS in AML study population	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]	0.463 (0.299, 0.717)	
p-value[b]	0.0002	
OS in *de novo* AML study population	N=38	N=18
Median survival, months (95% CI)	6.6 (3.7, 12.4)	4.3 (1.3, 10.7)
Hazard ratio (95% CI)[a]	0.670 (0.362, 1.239)	
p-value[b]	0.0991	
OS in secondary AML study population	N=40	N=20
Median survival, months (95% CI)	9.1 (4.4, 16.5)	4.1 (1.5, 6.4)
Hazard ratio (95% CI)[a]	0.287 (0.151, 0.548)	

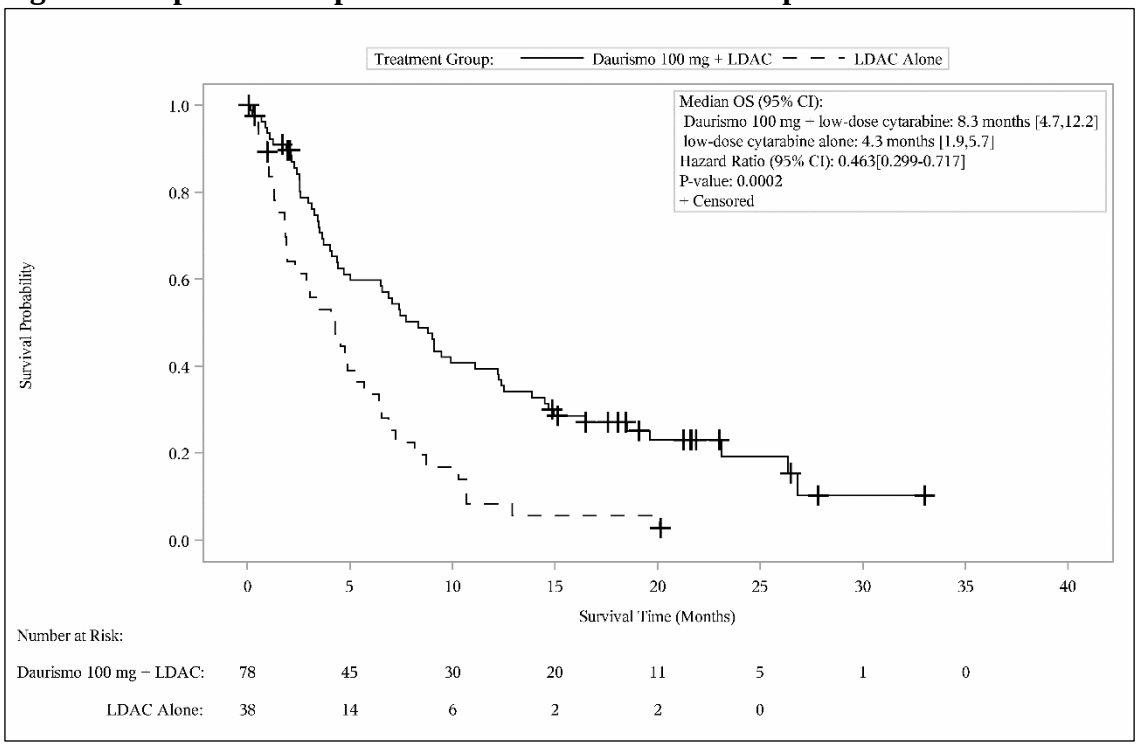
Endpoint/study population	Daurismo with low-dose cytarabine	Low-dose cytarabine alone
p-value[b]	< 0.0001	
Good/intermediate cytogenetic risk group	N=49	N=21
Median survival, months (95% CI)	11.1 (7.1, 14.9)	4.4 (1.8, 8.7)
Hazard ratio (95% CI)[a]	0.417 (0.233, 0.744)	
p-value[b]	0.0011	
Poor cytogenetic risk group	N=29	N=17
Median survival, months (95% CI)	4.4 (3.4, 9.1)	3.1 (1.1, 6.4)
Hazard ratio (95% CI)[a]	0.528 (0.273, 1.022)	
p-value[b]	0.0269	

Abbreviations: AML=acute myeloid leukaemia; CI=confidence interval; N=number of patients; OS=overall survival.

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

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

Figure 1. Kaplan-Meier plot of overall survival for AML patients



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

Improvement in OS was consistent across pre-specified subgroups by cytogenetic risk.

Based on investigator reported response, a numerically higher complete response (CR) rate (defined as absolute neutrophil count ≥ 1000/μl, platelet count ≥ 100,000/μl, < 5% bone marrow blasts, transfusion independent, and no extramedullary disease) was achieved for AML patients in the Daurismo with low-

dose cytarabine arm (17.9% [95% CI: 9.4%, 26.5%]) vs the low-dose cytarabine alone arm (2.6% [95% CI: 0.0%, 7.7%]).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Daurismo in all subsets of the paediatric population in treatment of AML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg dose of glasdegib, peak concentration in plasma is 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.

Food effect

After oral administration of glasdegib tablets, the mean absolute bioavailability is 77.1% compared to intravenous administration. Administration of glasdegib with a high-fat, high-calorie meal resulted in 16% lower exposure (AUC_{inf}) compared to overnight fasting. The impact of food on the pharmacokinetics of glasdegib is not considered clinically relevant. Glasdegib may be administered with or without food.

Following 100 mg once daily glasdegib dosing, the mean (coefficient of variation, %CV) of glasdegib C_{max} was 1252 ng/mL (44%) and AUC_{tau} was 17,210 ng•hr/mL (54%) in patients with cancer.

Distribution

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

Biotransformation

The primary metabolic pathways for glasdegib were comprised of N-demethylation, glucuronidation, oxidation, and dehydrogenation. 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.

In vitro interaction studies
In vitro CYP3A4 inhibition and induction
In vitro studies indicated that glasdegib is affected by inhibitors and inducers of CYP3A4. Please see section 4.5 for further discussion of moderate CYP3A4 inducers. A strong inhibitor of CYP3A4 increased the mean area under the curve (AUC_{inf}) by

~2.4-fold and maximum plasma concentration (C_{max}) by 40% of a single 200 mg oral dose of glasdegib in healthy subjects. A strong inducer of CYP3A4, reduced the mean AUC_{inf} by 70% and C_{max} by 35% of a single 100 mg dose of glasdegib in healthy subjects. Use of glasdegib with strong inducers should be avoided; caution should be use when administering concomitantly glasdegib with strong CYP3A4 inhibitors (see section 4.5).

Elimination

The mean (SD) plasma half-life of glasdegib was 17.4 3.7 hours after a single dose of 100 mg glasdegib in patients. The geometric mean oral clearance after multiple dosing was 6.45 L/hr. 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 faeces, 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 faeces accounted for 17.2% and 19.5% of the dose, respectively.

Linearity/non-linearity

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.

Special populations

Hepatic impairment
Data from a dedicated pharmacokinetic trial have shown that plasma exposures for total glasdegib (AUC_{inf} and C_{max}) were similar between subjects with normal hepatic function and subjects with moderate hepatic impairment (Child-Pugh Class B), whilst geometric mean AUC_{inf} and C_{max} values were 24% and 42% lower, respectively, for subjects with severe hepatic impairment (Child-Pugh Class C), compared to the normal hepatic function group. The glasdegib unbound exposure (unbound AUC_{inf}) is increased by 18% and 16% in subjects with moderate and severe impairment, respectively, relative to subjects with normal hepatic function. Peak glasdegib unbound exposure (unbound C_{max}) increased by 1%, for moderate hepatic impairment and decreased by 11% for severe hepatic impairment, relative to subjects with normal hepatic function. These changes are not considered to be clinically relevant.

Renal impairment
Data from a dedicated pharmacokinetic trial in subjects with varying degrees of renal function impairment indicate that total glasdegib exposure (AUC_{inf}) increased by 105%, and 102% with moderate (30 mL/min $\leq$ eGFR < 60 mL/min), and severe (eGFR < 30 mL/min) renal impairment, respectively, relative to subjects with normal (eGFR $\geq$ 90 mL/min) renal function. Peak glasdegib exposure (C_{max}) increased by 37%, and 20% for subjects with moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. These changes are not considered to be clinically relevant.

Elderly
In patients assigned to treatment with Daurismo with low-dose cytarabine (n=88; Study 1), 97.7% of the patients were aged 65 or older and 60.2% of the patients were aged 75 or older. Study 1 did not include a sufficient number of patients younger than age 65 to determine differences in adverse reactions reported from patients older than 65.

Age, race, gender, and body weight
There are limited data in patients younger than 65 years of age. Population pharmacokinetic analyses in adult patients (n=269) indicate that there are no clinically relevant effects of age, gender, race, body weight on the pharmacokinetics of glasdegib.

5.3 Preclinical safety data

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 alopecia, weight loss, 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 observation 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.

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.

Carcinogenicity studies have not been conducted with glasdegib.

In repeat-dose toxicity studies in rats, findings observed in the male reproductive tract included adverse testicular changes with glasdegib at doses 50 mg/kg/day, and consisted of minimal to severe hypospermatogenesis characterised 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). Safety margin for NOAEL (10 mg/kg/day) is 0.6, hence lower than clinically relevant.

In embryo-foetal developmental toxicity studies conducted in rats and rabbits, glasdegib was severely toxic to the conceptus as evidenced by complete resorption and/or abortion of foetuses, and teratogenic effects at lower dose levels. Teratogenic effects included 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, oedema, persistent truncus arteriosus, heart defects, absent lung, absent trachea, rib and vertebral abnormalities, and malformed or absent structures in the appendicular skeleton (notably the long bones). Severe developmental malformations were observed at maternal systemic exposures lower than the relevant human exposure at the recommended dose of 100 mg once daily.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Sodium starch glycolate
Microcrystalline cellulose (E460(i))
Calcium hydrogen phosphate (anhydrous) (E341ii)
Magnesium stearate (E470b)

Film-coating
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Triacetin (E1518)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC (polyvinyl chloride) blister sealed with aluminium foil containing 10 film-coated tablets, or high-density polyethylene (HDPE) bottle with polypropylene closure containing 30 film-coated tablets.

One carton contains 30 film-coated tablets in 3 blisters.
One carton contains 30 film-coated tablets in an HDPE bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1688

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/01/2025

10 DATE OF REVISION OF THE TEXT

30/01/2025