

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 25 mg film-coated tablets
Daurismo 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Daurismo 25 mg film-coated tablets

Each film-coated tablet contains glasdegib maleate equivalent to 25 mg of glasdegib.

Excipient with known effect

Each film-coated tablet contains 1.3 mg of lactose monohydrate.

Daurismo 100 mg film-coated tablets

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

Excipient with known effect

Each film-coated tablet contains 5.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Daurismo 25 mg film-coated tablets

7 mm round, yellow film-coated tablet debossed with “Pfizer” on one side and “GLS 25” on the other side.

Daurismo 100 mg film-coated tablets

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 and monitoring of laboratory and QT abnormalities

Complete blood counts, electrolytes, renal, and hepatic function should be assessed prior to the initiation of Daurismo and at least once weekly for the first month. Electrolytes and renal function should be monitored once monthly for the duration of therapy. Serum creatine kinase (CK) levels should be obtained prior to initiating Daurismo and as indicated clinically thereafter (e.g., if muscle signs and symptoms are reported). Electrocardiograms (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 QT corrected for heart rate (QTc) prolongation. ECG should be repeated if abnormal. Certain patients may require more frequent and ongoing ECG monitoring (see section 4.4). Abnormalities should be managed promptly.

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	<p>Assess electrolyte levels and supplement as clinically indicated.</p> <p>Review and adjust concomitant medicinal products with known QT prolonging effects (see section 4.5).</p> <p>Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation to less than or equal to 480 msec.</p>
Corrected QT interval greater than 500 msec	<p>Assess electrolyte levels and supplement as clinically indicated.</p> <p>Review and adjust concomitant medicinal products with known QT prolonging effects (see section 4.5).</p> <p>Interrupt Daurismo.</p> <p>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.</p> <p>Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation.</p> <p>Consider re-escalating the dose of Daurismo to 100 mg daily if an alternative aetiology for the QT prolongation can be identified.</p>
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]	<p>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.</p> <p>Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.</p>
Grade 2 without renal impairment (serum Cr ≤ ULN) [CK elevation >2.5 x ULN - 5 x ULN]	<p>Interrupt Daurismo and monitor CK levels weekly until resolution to baseline.</p> <p>Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume Daurismo at the same dose level and measure CK monthly thereafter.</p> <p>Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.</p> <p>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.</p>
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)]	<p>Interrupt Daurismo and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline.</p> <p>Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.</p> <p>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.</p>
Grade 2, 3 or 4 with renal impairment (serum Cr > ULN per CTCAE 4.0)	<p>If renal function is impaired, interrupt Daurismo and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment.</p> <p>Monitor CK and serum creatinine levels weekly until resolution to baseline.</p> <p>Monitor muscle symptoms for changes until resolution to baseline.</p> <p>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.</p>

Abbreviations: CK=creatinine 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 $10 \times 10^9/L$ for more than 42 days in the absence of disease	Discontinue Daurismo and low-dose cytarabine permanently.
Neutrophil count less than $0.5 \times 10^9/L$ 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).

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 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 ($\geq 20\%$) 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 (25.0%), abdominal pain (25.0%), rash (25.0%), dyspnoea (25.0%), 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 ($\geq 1/10$) and common ($\geq 1/100$ 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)

System organ class	Preferred term	All grades		
		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	0.0
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	25.0	7.1
Gastrointestinal disorders	Nausea	Very common	35.7	2.3
	Diarrhoea	Very common	28.5	4.7
	Constipation	Very common	25.0	1.1
	Abdominal pain ^d	Very common	25.0	0.0
	Vomiting	Very common	21.4	2.3
	Stomatitis	Common	4.7	0.0
Skin and subcutaneous tissue disorders	Rash ^e	Very common	25.0	2.3
	Alopecia	Very common	10.7	0.0
Musculoskeletal and connective tissue disorders	Muscle spasms ^f	Very common	30.9	5.9
	Arthralgia	Very common	11.9	0.0
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	0.0
Investigations	Platelet count decreased	Very common	16.6	16.6
	White blood cell count decreased	Very common	15.4	13.0
	Neutrophil count decreased	Very common	13.0	13.0

^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 the national reporting system listed in Appendix V.

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 (%)		
<i>De Novo</i> 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

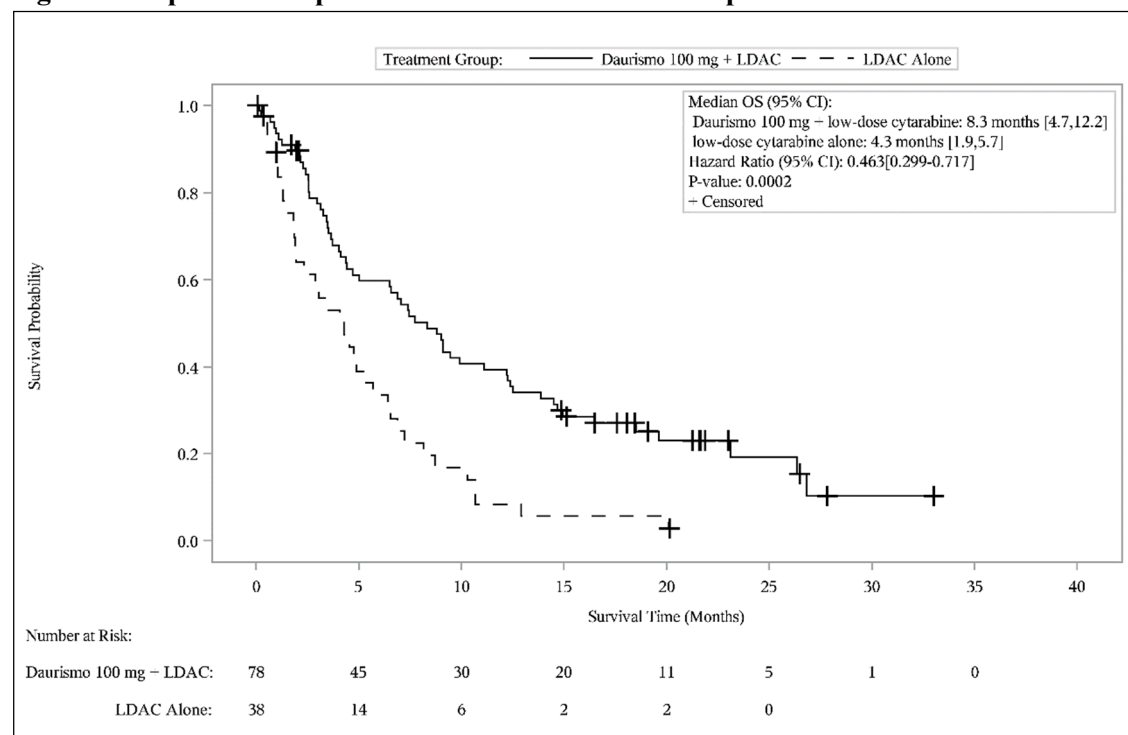
Endpoint/study population	Daurismo with low-dose cytarabine	Low-dose cytarabine alone
OS in AML study population	N=78	N=38
Median survival, months (95% CI)	8.3 (4.7, 12.2)	4.3 (1.9, 5.7)
Hazard ratio (95% CI) ^a	0.463 (0.299, 0.717)	
p-value ^b	0.0002	
OS in <i>de novo</i> AML study population	N=38	N=18
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)	
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 $\geq 1000/\mu\text{l}$, platelet count $\geq 100,000/\mu\text{l}$, $< 5\%$ 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 1,252 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 (V_z/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 CYP inhibition and induction

In vitro studies indicated that glasdegib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 at clinically relevant concentrations. *In vitro* studies indicated that glasdegib is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

In vitro studies of UGT inhibition

In vitro studies indicated that glasdegib is not an inhibitor of uridine-diphosphate glucuronosyltransferase (UGT)1A4, UGT1A6, UGT2B7, and UGT2B15 at clinically relevant concentrations. Glasdegib may have the potential to inhibit UGT1A1, and possibly UGT1A9, however, clinically relevant drug-drug interactions are not expected.

In vitro studies of organic anion and cation transporter inhibition

In vitro studies indicated that glasdegib is not an inhibitor of organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, at clinically relevant concentrations.

Elimination

The mean (\pm 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_{τ}) 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 ($30 \text{ mL/min} \leq \text{eGFR} < 60 \text{ mL/min}$), and severe ($\text{eGFR} < 30 \text{ mL/min}$) renal impairment, respectively, relative to subjects with normal ($\text{eGFR} \geq 90 \text{ mL/min}$) 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 Pre-clinical 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) (100 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 or 60 film-coated tablets.

Daurismo 25 mg film-coated tablets

One carton contains 60 film-coated tablets in 6 blisters.
One carton contains 60 film-coated tablets in an HDPE bottle.

Daurismo 100 mg 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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Daurismo 25 mg film-coated tablets

EU/1/20/1451/001

EU/1/20/1451/002

Daurismo 100 mg film-coated tablets

EU/1/20/1451/003

EU/1/20/1451/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

The MAH shall ensure that in each Member State where DAURISMO is marketed, all male patients are provided via their prescribing physicians with the Patient Alert Card. The Patient Alert Card should contain the following key elements:

- Glasdegib may be present in semen carrying a potential risk of reproductive and developmental toxicity
- Effective contraception (condom with spermicide, if available) should be used, even after vasectomy and for at least 30 days after the last dose due to the potential risk of exposure of male patients' female partners to glasdegib through semen

- The importance of informing a healthcare provider as soon as a pregnancy is suspected, either for a female patient or female partner of a male patient
- A reminder not to donate semen while taking Daurismo and for 30 days after last dose
- The recommendation to seek advice on effective fertility preservation for men prior to initiating treatment with glasdegib.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 25 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 25 mg film-coated tablets
glasdegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains glasdegib maleate equivalent to 25 mg of glasdegib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1451/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daurismo 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABELS – 25 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 25 mg film-coated tablets
glasdegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains glasdegib maleate equivalent to 25 mg of glasdegib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1451/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daurismo 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – 25 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 25 mg tablets
glasdegib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 100 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 100 mg film-coated tablets
glasdegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains glasdegib maleate equivalent to 100 mg of glasdegib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1451/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daurismo 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 100 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 100 mg film-coated tablets
glasdegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains glasdegib maleate equivalent to 100 mg of glasdegib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1451/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daurismo 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – 100 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Daurismo 100 mg tablets
glasdegib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Daurismo 25 mg film-coated tablets **Daurismo 100 mg film-coated tablets** glasdegib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Daurismo is and what it is used for
2. What you need to know before you take Daurismo
3. How to take Daurismo
4. Possible side effects
5. How to store Daurismo
6. Contents of the pack and other information

1. What Daurismo is and what it is used for

Daurismo is a cancer medicine containing the active substance glasdegib.

Daurismo is used with another cancer medicine, cytarabine, to treat adults newly diagnosed with a blood cancer called acute myeloid leukaemia (AML).

How Daurismo works

In AML, cancer cells called stem cells constantly make new leukaemic cancer cells. Daurismo works by blocking a key process in these stem cells, called the Hedgehog (Hh) pathway. This reduces their ability to make new cancer cells. By blocking the Hh pathway, Daurismo can also make cancer cells more sensitive to a cancer medicine, cytarabine, used to treat AML. Combining Daurismo with the medicine cytarabine may increase how long patients are likely to live by decreasing growth of the cancer and possibly by increasing cancer cell death.

If you have any questions about how Daurismo works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Daurismo

Do not take Daurismo

- if you are allergic to glasdegib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Daurismo

- if you or your partner are able to become pregnant (see section Pregnancy, breast-feeding and fertility).
- if you have ever had QT interval prolongation (a change in electrical activity of the heart that can cause serious irregular heart rhythms) or know you are at danger of the condition.
- if you take other medicines that you have been told can prolong QT interval.
- if blood tests show you have abnormal levels of electrolytes (e.g. calcium, magnesium, potassium).
- if you have kidney problems.
- if you have a history of muscle cramps or weakness.

Tell your doctor immediately while taking this medicine

- if your muscles hurt or you have unexplained muscle cramps or weakness during treatment with Daurismo. Your doctor may need to change your dose, or stop your treatment temporarily or permanently.

Children and adolescents

Daurismo is not to be used in patients less than 18 years of age.

Other medicines and Daurismo

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Daurismo can affect the way some other medicines work. Some other medicines can affect the way Daurismo works.

In particular, the following may increase the risk of side effects with Daurismo:

- boceprevir – a medicine used to treat hepatitis C.
- cobicistat, ritonavir, telaprevir – medicines used to treat HIV infection.
- itraconazole, ketoconazole, voriconazole, posaconazole – medicines used to treat fungal infections.
- troleandomycin – a medicine used to treat bacterial infections.
- conivaptan – a medicine used to regulate imbalance of water and salt.
- amiodarone, disopyramide, dofetilide, ibutilide, sotalol, quinidine – medicines used to treat heart problems.
- droperidol, haloperidol, pimozide – medicines used to treat psychotic diseases.
- moxifloxacin – a medicine used to treat a certain type of bacterial infections.
- methadone – a medicine used to treat pain and for the treatment of opioid addiction.

The following medicines may reduce the effectiveness of Daurismo:

- carbamazepine, phenytoin, anti-epileptics – medicines used to treat seizures or fits.
- rifampicin – a medicine used to treat tuberculosis (TB).
- St. John's wort (*Hypericum perforatum*) – a herbal product used to treat mild depression and anxiety.
- enzalutamide – a medicine used to treat prostate cancer.
- mitotane – a medicine used to treat adrenal gland cancer.
- bosentan – a medicine used to treat high blood pressure.
- efavirenz, etravirine – medicines used to treat HIV infection.
- modafinil – a medicine used to treat sleep disorders.
- nafcillin – a medicine used to treat certain types of bacterial infections.

Daurismo with food and drink

Do not drink grapefruit juice or eat grapefruit while on treatment with Daurismo as it may change the amount of Daurismo in your body.

Pregnancy, breast-feeding and fertility

Pregnancy

You must not become pregnant while taking Daurismo and you must not take it if you are pregnant. Daurismo can cause severe birth defects in babies or lead to the death of an unborn baby.

Your doctor will give you more information about the effects of Daurismo on the unborn baby and will carry out a pregnancy test before you start taking the medicine.

You must talk to your doctor immediately if you or your partner become pregnant or suspect you could be pregnant during treatment and for 30 days after your last dose of Daurismo. If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Contraception in women and men

Women

You should always use effective birth control (contraception) while taking Daurismo and for at least 30 days after the last dose of Daurismo. Talk to your doctor about birth control methods that are right for you and your partner.

Men

Men should always use effective contraception, including condoms (with spermicide, if available), even if you have had a vasectomy, while taking Daurismo and for at least 30 days after the last dose of Daurismo.

You should not donate semen at any time while you are taking Daurismo and for at least 30 days after your last dose.

Breast-feeding

Do not breast-feed while taking Daurismo or during the one week after the last dose of Daurismo. It is not known if Daurismo passes into your breast milk and harms your baby.

Fertility

Daurismo may affect male and female fertility. Talk to your doctor about fertility preservation before taking Daurismo.

Driving and using machines

If you feel tired, or get muscle cramps, pain or nausea (feeling sick) while on treatment with Daurismo, take special care when driving and using machines.

Daurismo contains sodium

This medicine contains less than 1 mmol sodium (less than 23 mg) per tablet, that is to say Daurismo is essentially 'sodium -free'.

Daurismo contains lactose

This medicine contains lactose (found in milk or dairy products).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Daurismo

Take Daurismo once a day at about the same time every day. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet of 100 mg taken by mouth once a day with or without food.

If you get certain side effects while you are taking Daurismo (see section 4 “Possible side effects”), your doctor may lower your dose or stop treatment, either temporarily or permanently.

If you vomit after taking Daurismo

If you vomit after taking a dose of Daurismo, do not take an extra dose, just take your next dose at the usual time.

If you take more Daurismo than you should

If you accidentally take too many tablets, tell your doctor, pharmacist or nurse right away. You may require urgent medical attention.

If you forget to take Daurismo

If you forget to take a tablet, then take it as soon as you remember unless more than 10 hours have passed since the scheduled dose time, in which case, you should skip the dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Daurismo

Do not stop taking Daurismo unless your doctor tells you to.

It is important to take Daurismo every day, as long as your doctor prescribes it to you. If you cannot take the medicine as your doctor has prescribed, or you feel you do not need it anymore, speak with your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Daurismo may cause severe birth defects. It may also lead to the death of a baby before it is born or shortly after being born. You must not become pregnant while taking this medicine (see section 2, “What you need to know before you take Daurismo”).

Other side effects with Daurismo, in combination with cytarabine, include:

Very common: may affect more than 1 in 10 people

- low haemoglobin
- bleeding
- fever
- nausea
- loss of appetite
- muscle pain
- feeling tired
- decrease in the number of platelets in the blood
- diarrhoea
- pneumonia
- changes in taste
- swelling of arms and legs
- constipation
- abdominal (belly) pain
- rash
- shortness of breath
- vomiting
- weight loss

- decrease in the number of white blood cells
- decrease in the number of a type of white blood cells (neutrophils)
- joint pain
- hair loss

Common: may affect up to 1 in 10 people

- changes in the electrical activity of the heart
- heart palpitations
- blood infection
- burning sensation during urination and frequent and urgent need to urinate (may be symptoms of urinary tract infection)
- mouth irritation

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Daurismo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister foil or bottle after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Daurismo contains

- The active substance is glasdegib.
Daurismo 25 mg film-coated tablets: each film-coated tablet contains glasdegib maleate equivalent to 25 mg of glasdegib.
Daurismo 100 mg film-coated tablets: each film-coated tablet contains glasdegib maleate equivalent to 100 mg glasdegib.
- The other ingredients are:
Tablet core: sodium starch glycolate, microcrystalline cellulose, calcium hydrogen phosphate anhydrous, and magnesium stearate. See section 2 “Daurismo contains sodium.”
Film-coating: lactose monohydrate, hypromellose, titanium dioxide, macrogol, triacetin, iron oxide yellow, and iron oxide red (100 mg tablets only). See section 2 “Daurismo contains lactose.”

What Daurismo looks like and contents of the pack

Daurismo 25 mg film-coated tablets

- Round, yellow film-coated tablets, debossed with “Pfizer” on one side and “GLS 25” on the other side.
- Provided in blisters of 10 tablets. Each pack contains 60 tablets in either 6 blisters or in one plastic bottle.

Daurismo 100 mg film-coated tablets

- Round, pale orange film-coated tablets, debossed with “Pfizer” on one side and “GLS 100” on the other side.
- Provided in blisters of 10 tablets. Each pack contains 30 tablets in either 3 blisters or in one plastic bottle.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.