Date: 20 November 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Daurismo

International non-proprietary name: glasdegib
Pharmaceutical form: film-coated tablets
Dosage strength: 25 mg and 100 mg
Route(s) of administration: oral use
Marketing Authorisation Holder: Pfizer AG
Marketing Authorisation No.: 67473
Decision and Decision date: rejected on 22 September 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AEs	Adverse events
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukaemia
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ELN	European LeukemiaNet
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HDPE	High Density Polyethylene
HMAs	Hypomethylating agents
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LDAC	Low-dose cytarabine
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MDS	Myelodysplastic syndrome
Min	Minimum
mOS	Median overall survival
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OS	Overall survival
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	once daily
RMP	Risk Management Plan
SC	subcutaneous
SwissPAR	Swiss Public Assessment Report
TEAEs	Treatment emergent adverse events
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance glasdegib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 13 May 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Requested Dosage

Recommended dose: 100 mg orally, once daily in combination with low-dose cytarabine.

2.3 Regulatory History (Milestones)

Application	27 May 2019
Formal control completed	21 June 2019
List of Questions (LoQ)	5 November 2019
Answers to LoQ	31 January 2020
Predecision	1 May 2020
Final Decision	22 September 2020
Decision	refusal

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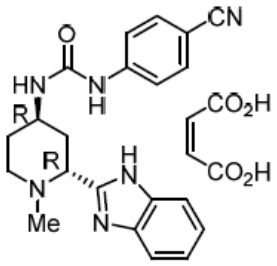
3 Medical Context

Acute Myeloid Leukaemia (AML) is a myelopoietic blood and bone marrow neoplasia characterised by clonal expansion of various cells of myeloid lineage in blood, bone marrow and other tissues. The therapeutic approach in young and/or fit patients is curative. For older and unfit patients who are not candidates for standard induction chemotherapy, less intensive treatment options are low-dose cytarabine (LDAC) and hypomethylating agents. However, hypomethylating agents are currently the preferred treatment regimen for older and unfit patients who are not candidates for standard induction chemotherapy.

4 Quality Aspects

4.1 Drug Substance

INN: Glasdegib
Chemical name: 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate
Molecular formula: $C_{21}H_{22}N_6O$ (drug), $C_4H_4O_4$ (maleate)
Molecular mass: 490.51
Molecular structure:



Glasdegib is a white to pale-coloured powder. Glasdegib is slightly soluble in water. Glasdegib has two asymmetric centres. The absolute configuration is 2R, 4R. Only one crystalline anhydrous form of glasdegib maleate has been identified and assigned Form 1.
The drug substance is manufactured by a multi-step chemical synthesis with final isolation by crystallisation.
The structure of glasdegib has been fully elucidated using several spectroscopic techniques.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities, particle size and water content.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

The finished product is available as immediate-release film-coated tablets, provided at 25 and 100 mg strengths. The 25 mg tablets are presented as round, yellow film-coated tablets debossed with “Pfizer” on one side and “GLS” over “25” on the other side. The 100 mg tablets are presented as round, pale orange film-coated tablets debossed with “Pfizer” on one side and “GLS” over “100” on the other side.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Satisfactory validation data pertaining to the commercial manufacturing process are provided.

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The drug product specification covers appropriate parameters for this dosage form and includes relevant physicochemical, identification, assay and purity tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The drug product is packaged into HDPE bottles and PVC-Alu blisters.
Appropriate stability data have been generated in the packaging materials intended for commercial use and following relevant international guidelines. The data show good stability of the finished product and support the proposed shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Daurismo (active ingredient: glasdegib) Swissmedic conducted an abridged evaluation, which referred to the FDA's approval on November 21, 2018 and relied on FDA's Nonclinical Review (Report of October 26, 2018), and the Day 120 Responses to EU List of Questions provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Daurismo in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The safety issues identified in the nonclinical studies are similar to those of other approved hedgehog-signalling pathway inhibitors.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The available assessment reports and respective product information from the US FDA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose Finding and Dose Recommendation

The recommended phase 2 dose of 100 mg once daily (QD) was chosen based on the safety results of the Phase 1 part of the B1371003 study. Of particular relevance for the reduced dose of 100 mg QD was the interaction potential with CYP3A4 inhibitors.

6.3 Efficacy

Phase 2 of the pivotal study B1371003 was an open-label, randomised (2:1), multinational (USA and Europe) trial of orally administered glasdegib in combination with low-dose cytarabine (LDAC) in subjects with acute myeloid leukaemia (de novo and secondary) or high-risk myelodysplastic syndrome (MDS). The clinical review focused on unfit AML patients according to the requested indication.

AML patients received glasdegib (100 mg orally once daily) with LDAC (20 mg SC twice daily on days 1 to 10 of the 28-day cycle) (n=78) or LDAC alone (n=38) in 28-day cycles until disease progression or unacceptable toxicity.

Glasdegib was combined with LDAC, which is not the preferred treatment according to the National Comprehensive Cancer Network (NCCN), *Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie* (DGHO) and European LeukemiaNet (ELN) guidelines. Hypomethylating agents (HMAs) are the current standard of care according to international guidelines. Treatment with LDAC is an alternative treatment option if there are contraindications to HMAs. However, at the time of study initiation, HMAs were not licensed in Switzerland for the treatment of unfit patients with AML. Therefore, the combination of glasdegib with LDAC and the control arm with LDAC in study B1371003 is acceptable. However, currently available and recommended treatment options, published efficacy and safety results for HMAs were also taken into consideration for the benefit-risk evaluation.

The primary endpoint of Overall Survival (OS) was analysed by the Kaplan-Meier method on the AML and MDS population using the stratified log-rank test (one-sided α=10%), estimating hazard ratio (HR) and its 80% CI to compare glasdegib+LDAC and LDAC alone with a power of 80% to detect the difference in both arms. The analysis of unfit AML subjects was not pre-specified in the statistical analysis plan. A gatekeeping testing procedure to control for an overall type I error at 1-sided α=0.10 for OS in the AML+MDS and OS in the AML subpopulation was added retrospectively. Therefore, study B1371003 is considered as an exploratory trial from a regulatory point of view.

In the glasdegib+LDAC arm AML patients had a median age of 77 years, 76% were male and 96% white. Overall, 89% in the glasdegib+LDAC arm had AML, of these 49% had de novo AML and 51% secondary AML.

In the AML subpopulation relevant baseline imbalances were observed, in particular relevant differences were present for patients with poor cytogenetic risk (37% vs. 45%) and with adverse ELN prognostic risk factors (32% vs 42%) between the glasdegib+LDAC arm and LDAC alone arm, respectively. These differences are of prognostic relevance and a “selection bias” in favour of the verum arm cannot be excluded.

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Results

1. Overall survival results before adjusting for baseline imbalances (data cut-off from 3 April 2019)
In the subpopulation of unfit AML patients, the median overall survival in the glasdegib+LDAC arm was 8.3 versus 4.3 months for LDAC alone with an HR of 0.53 (CI 95% 0.35, 0.8, p-value 0.0012).

Patients with a good/intermediate cytogenetic risk presented a median OS (mOS) of 11.1 months in the glasdegib+LDAC arm versus 4.3 months in the control arm (HR 0.417 CI 95% 0.233, 0.744). For AML patients with poor cytogenetic risk the mOS was 4.4 months in the glasdegib+LDAC arm versus 2.1 months in the control arm (HR 0.51, CI 95% 0.26, 1.00, p-value 0.022).

It cannot be excluded that the imbalances in baseline characteristics had an impact on the results with a disadvantage for the LDAC control arm.

2. Overall survival results after adjusting for baseline imbalances (data cut-off from 3 January 2017)
After adjusting for baseline characteristics, the results of OS present inconsistencies depending on the cytogenetic risk with relevant impact on the robustness of the OS results. After adjusting for baseline imbalances with Inverse Probability of Treatment Weighting (IPTW) using Average Treatment Effect in the Treated (ATT), patients with poor cytogenetic risk treated with glasdegib+LDAC presented no OS benefit compared to LDAC alone (glasdegib+LDAC: 4.4 months versus LDAC: 4.9 months). The hazard ratio of 0.579 (CI 95% 0.319, 1.054) demonstrates a further shift of the upper limit of the confidence interval that is disadvantageous for glasdegib+LDAC.

6.4 Safety

The overall safety profile for glasdegib is based on data from study B1371003 in 84 patients with AML (n=75) and high-risk MDS (n=9). The median exposure to glasdegib+LDAC across the dataset was 75.5 days (data cut-off from 3 January 2017). The median duration of treatment was 83 days in the glasdegib+LDAC arm compared to 47 days in the LDAC alone arm.

The most common treatment emergent adverse events (TEAEs) in these patients were anaemia (45%), febrile neutropenia (36%), nausea (36%), decreased appetite (33%), fatigue (31%), thrombocytopenia (31%), pneumonia (29%), diarrhoea (27%), pyrexia (27%), peripheral oedema (26%), constipation (25%), dysgeusia (25%), dyspnoea (25%), muscle spasms (23%), cough (21%), dizziness (21%), vomiting (21%).

Grade 3-4 TEAEs were more frequent in the glasdegib+LDAC arm compared to LDAC alone (64% vs 56%), mainly due to cytopenic events (anaemia, febrile neutropenia, thrombocytopenia). Of special concern were QT interval prolongations, which occurred more frequently in the glasdegib+LDAC arm (20% vs 10%), as well as serious QT interval prolongation (10% vs 0%) and grade 3-4 AEs (13% vs 5%). Of particular concern are cardiac grade 5 AEs such as sudden death, cardiac arrest and myocardial infarction that occurred only in the glasdegib+LDAC arm.

Furthermore, nervous system disorders (58% vs 24%) were more frequent in the glasdegib+LDAC arm, mainly due to increase of dysgeusia. Taking into account the different exposure of glasdegib+LDAC and LDAC alone, more patients treated with glasdegib+LDAC experienced muscle spasms and creatinine phosphokinase increase. Renal toxicities (23% vs 15%) and skin disorders (52% vs 34%), in particular rash and alopecia, were also more common in the glasdegib+LDAC arm.

Only limited data are available for the evaluation of long-term safety of glasdegib+LDAC. Especially in such a vulnerable elderly patient population with comorbidities, adequate long-term data with an acceptable safety profile are necessary for a positive benefit-risk evaluation.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Unfit patients with AML who are not candidates for standard induction chemotherapy have limited treatment options. There is an unmet medical need for new efficacious and safe treatment regimens for this patient population.

For the evaluation of efficacy and safety, the results from one pivotal phase 1/2 study, B1371003, was submitted.

In conclusion, the benefit-risk balance of glasdegib+LDAC in the claimed indication was negative. The main reasons for the negative benefit-risk were as follows:

- Insufficient submission of phase 1/2 clinical data to establish the efficacy of glasdegib+LDAC.
    - Statistical aspects with the submission of one study with insufficient type 1 error control (1-sided alpha 0.1, retrospectively added gatekeeping) in a small, previously unspecified patient population.
    - Imbalances in baseline characteristics that were disadvantageous to the control arm and affecting the OS results.
    - After adjusting for baseline imbalances, inconsistencies in OS results depending on the cytogenetic risk were apparent.
- Treatment with glasdegib+LDAC is associated with significant toxicity, and only limited long-term safety data are available.
- OS results are comparable with those for approved standard therapies in Switzerland that have an established safety profile and long-term safety data based on randomised phase III trials.

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