EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

GLASDEGIB 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

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V0.1	**14/11/2019**	Incorporation of survey results
V0.2	**03/12/2019**	Incorporation of dedicated reviewer comments
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V1.0	**06/05/2020**	Final Project Plan

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Assessment team

Author(s)	Austrian Social Insurance (DVSV), Austria
Co-Author(s)	National Centre for Pharmacoeconomics (NCPE), Ireland
Dedicated Reviewer(s)	French National Authority for Health (HAS), France National Authority of Medicines and Health Products (INFARMED), Portugal Swiss Network for HTA (SNHTA), Switzerland

For further information on the work distribution and further contributors, please see section 4.1.

Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

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LIST OF ABBREVIATIONS

AE	Adverse event
AML	Acute myeloid leukaemia
ASI	Austrian Social Insurance
CHMP	Committee for Medicinal Products for Human Use
CR	Complete Remission
CSR	Clinical Study Reports
DOICU	Declaration of Interest and Confidentiality Undertaking
DVSV	Austrian Social Insurance
EFF	Effectiveness domain
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
HAS	French National Authority for Health
HTAi	Health Technology Assessment international
INFARMED	National Authority of Medicines and Health Products
LDAC	Low-dose cytarabine
NCPE	National Centre for Pharmacoeconomics
PICO	Population, intervention, control, outcome
pMAH	Prospective Marketing Authorisation Holder
SAF	Safety domain
SNHTA	Swiss Network for HTA
ZIN	Zorginstituut Nederland

1 INTRODUCTION

On 17-07-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of glasdegib (Pfizer) agreed that EUnetHTA will perform a joint relative effectiveness assessment of glasdegib 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. Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national processes supporting reimbursement and pricing decisions.

2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of glasdegib in the target patient population with relevant comparators. The target patient population and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

The following table provides the scope (i.e. Population – Intervention – Control – Outcome (PICO) question) identified for the assessment of glasdegib.

Table 2.1: Assessment scope: relevant PICO(s) identified for the planned assessment.

Description	Assessment scope
Population	Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are not eligible for standard induction chemotherapy ICD-10: 92.0 MeSH-terms: Leukemia, Myeloid, Acute Tree Number(s): C04.557.337.539.275 MeSH Unique ID: D015470
Intervention	Glasdegib 100 mg orally once daily continuously (on days 1 to 28) in combination with low-dose cytarabine (LDAC) Synonyms for glasdegib: PF-04449913
Comparison	• Azacitidine • Decitabine • LDAC • Best Supportive Care (hydroxyurea, transfusion support,..)[1]
Outcomes	Effectiveness[2]: • Overall survival • Health-related quality of life • Transfusion independency • Objective Response: Overall Response Rate: Complete Remission (CR) + CR with incomplete blood count recovery + morphologic leukaemia-free state Safety[3]: • Serious adverse events (AEs) • Grade ≥3 AEs • Fatal AEs • Overall AE • AEs of special interest (febrile neutropenia, pneumonia, haemorrhage, QT Interval Prolongation) • Treatment discontinuation due to AE
Study type	Effectiveness: • Randomised controlled trials Safety: • If suitable evidence syntheses (SRs/HTA reports) are available: • evidence syntheses (SRs/HTA reports); and • primary studies (as described in next bullet) published after the last search date of the latest SR/HTA document. If suitable evidence syntheses (SRs/HTA reports) are NOT available: • Randomised controlled trials; • Non-randomised controlled trials; • Observational studies

[1] All comparators were explicitly mentioned by patient organizations
[2] Including data at 6 and 12 months
[3] Including data at 90 days

3 METHODS

The EUnetHTA Guidelines [1-10], available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

3.1 Inclusion criteria

During the assessment the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment. In addition, only studies available in English will be considered in this assessment since this is the common language for the countries involved and most often the language used in relevant publications and reports to be assessed.

3.2 Information retrieval

The assessment will be based on a submission dossier provided by the pMAH. To allow for a meaningful assessment, the submission dossier has to be complete with regard to the available evidence relevant for the research question. This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2 [7]. The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the submission dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's submission dossier will be checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. If there are major flaws in the search conducted by the manufacturer, further supplementary searches, as appropriate, will be conducted to check for possible incompleteness of the study pool. The search date, complete search strategies and the search results will be reported in the assessment. However, if the evidence provided in the submission dossier is incomplete it will not be supplemented by analyses by the authors of the assessment. The incompleteness and its consequences for the conclusions of the report will be described in the assessment report.

3.3 Data analysis and synthesis

The assessment will be based on the data and analyses included in the submission dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the submission dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the assessment report according to the research questions defined in Section 2.

3.3.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the submission dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the submission dossier.

3.3.2 Assessment of risk of bias

The assessment of risk of bias will follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials [8] and non-randomised studies on interventions [9]. The risk of bias of the results of each included study will be described separately for each patient-relevant outcome. For this purpose, risk of bias will be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high, this will not lead to exclusion of the corresponding data. Rather, the risk-of-bias classification should inform the discussion on heterogeneous study results and the determination of certainty of results.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the submission dossier will be evaluated. Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment will be presented in the assessment report.

3.3.3 Description of design and results of individual studies

During the assessment, the information in the Submission Dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the Assessment Report.

3.3.4 Synthesis of study results

Meta-analyses

If several studies are available for the same PICO, they should be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view [10].

During the assessment, the methods applied for the meta-analyses presented in the Submission Dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the Assessment Report.

Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the Submission Dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

Indirect comparisons

If indirect comparisons are included in the Submission Dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated [10]. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the Assessment Report.

3.4 Patient involvement

At the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asked general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment. The questions were based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

European and national patient organisations had to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' referred to anyone living with, or who has lived with, the condition for which the new medicine is indicated. Three patient organisations completed the survey, namely Leukaemia Care (United Kingdom), Association of Cancer Patients in Finland (Finland) and Deutsche Leukämie- & Lymphom-Hilfe (Germany).

The information gathered from the open call was used to inform the scope of this assessment and a summary of the input received will be provided in the assessment report.

4 PROJECT ORGANISATION

4.1 Participants

Table 4-1: Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	Austrian Social Insurance (DVSV)	Austria	• Develop first draft and final version of EUnetHTA project plan with co-author • Relative effectiveness and safety assessment • Send "draft versions" to reviewers/pMAHs, compile feedback and perform changes according to comments on Results section • Prepare the final assessment including a final summary of the assessment in collaboration with the co-authors
Co-Author	National Centre for Pharmacoeconomics (NCPE)	Ireland	• Contribute to project plan development • Contribute to Methods section • Compile the background section • Incorporate reviewers/pMAHs comments on background section of draft assessments • Check and validate Results section
Information specialist	Swiss Network for HTA (SNHTA)	Switzerland	Review of information retrieval, conduct of searches required for checking completeness of information retrieval in submission dossier; reporting information retrieval check in the assessment report
Statistical specialist	DVSV, NCPE	Austria, Ireland	Expert review of statistical analyses presented in submission dossier, statistical support for authors
Dedicated Reviewer	French National Authority for Health (HAS)	France	Review draft project plan and first draft of assessment report
Dedicated Reviewer	National Authority of Medicines and Health Products (INFARMED)	Portugal	Review draft project plan and first draft of assessment report
Dedicated Reviewer	Swiss Network for HTA (SNHTA)	Switzerland	Review draft project plan and first draft of assessment report
Contributors			
Patient organisations	Leukaemia Care Association of Cancer Patients in Finland Deutsche Leukämie- & Lymphom-Hilfe	UK Finland Germany	Complete the EUnetHTA open call in order to inform the scope of the assessment
Medical Editor	*TBC*	*TBC*	Responsible for the medical editing of the report
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	Role in the project
Pfizer Inc.	Manufacturer (MAH); Completing the submission dossier; Fact check of the draft assessment report

4.3 Milestones and deliverables

Table 4-3: Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**17-07-2019**	**30-07-2020**
Letter of Intent received	17-07-2019	
Scoping phase	**03-10-2019**	**30-04-2020**
Scoping PICO and development of first draft Project Plan	03-10-2019	15-11-2019
PICO survey – request relevant PICO from Member States	14-10-2019	24-10-2019
Adapt draft Project Plan based on PICO survey	04-11-2019	15-11-2019
Open call for patient input	11-10-2019	27-12-2019
Review of first draft Project Plan	18-11-2019	26-11-2019
Development of second draft Project Plan & answers to DR comments	28-11-2019	13-12-2019
Receive Scoping F2F meeting documents from pMAH	20-12-2019	
Pre-scoping e-meeting with the Assessment Team	09-01-2020	
Share discussion topics for Scoping F2F Meeting	23-01-2020	
Scoping F2F meeting with manufacturer	30-01-2020	
Share action points from F2F meeting with manufacturer	06-02-2020	
(pre-)Assessment phase	**01-04-2020**	**30-04-2020**
Receive Submission Dossier from pMAH	31-03-2020	
Check formal completeness of Submission Dossier	01-04-2020	10-04-2020
Receive missing items and comments on the requests from the formal completeness check from pMAH	17-04-2020	
Start writing Assessment (background, methods)	13-04-2020	30-04-2020
CHMP opinion	30-04-2020	
Finalize Project Plan	05-05-2020	
Assessment phase	**30-04-2020**	**30-07-2020**
Writing first draft Joint Assessment	30-04-2020	09-06-2020
Review by DRs (and if applicable include experts)	10-06-2020	19-06-2020
Writing second draft Joint Assessment	22-06-2020	10-07-2020
Medical Editing	13-07-2020	17-07-2020
Fact Check by pMAH (parallel with medical editing)	13-07-2020	17-07-2020
Final Assessment + response Fact Check	28-07-2020	
Expected EPAR	*24-07-2020*	
Publication final version of rapid assessment	29-07-2020	30-07-2020

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