EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

CRIZANLIZUMAB INDICATED FOR THE PREVENTION OF RECURRENT VASO-OCCLUSIVE CRISES IN SICKLE CELL DISEASE PATIENTS AGED 16 YEARS AND OVER

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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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LIST OF ABBREVIATIONS

ACS	Acute chest syndrome
ADL	Activities of daily living
BPI	Brief Pain Inventory
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Reports
DOI	Declaration of Interest
DR	Dedicated Reviewers
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
HbSC	Sickle cell/haemoglobin C
HbSS	Homozygous sickle cell anaemia
HbSβ^+	Sickle cell/β^+ thalassemia
HbSβ^0	Sickle cell/β^0 thalassemia
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
HU/HC	Hydroxyurea/hydroxycarbamide
PICO	Population, intervention, control, outcome
pMAH	Prospective Marketing Authorisation Holder
PTJA	Pharmaceutical Joint Assessment
QoL	Quality of life
RBC	Red blood cells
REA	Relative Effectiveness Assessment
SCD	Sickle cell disease
VOC	Vaso-occlusive crisis
WP4	Work Package 4

1 INTRODUCTION

On 13-06-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of crizanlizumab (Novartis) agreed that EUnetHTA will perform a joint relative effectiveness assessment of crizanlizumab indicated for the prevention of vaso-occlusive crises in sickle cell disease patients aged 16 years and over. 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.

1.1 Pathophysiology

Sickle cell disease (SCD) belongs to a group of inherited red blood cells disorders called haemoglobinopathies, in which the globin chain of the haemoglobin can be affected in a qualitative (structure abnormalities) or quantitative way. SCD is characterised by the abnormal formation of haemoglobin due to a point mutation in the β-globin gene. The abnormal haemoglobin easily polymerises into a “sickle” shape (sickle haemoglobin; HbS), leading to rigidity of the red blood cells (RBC), increased viscosity of the blood and vaso-occlusion. Furthermore, HbS binds less oxygen than normal haemoglobin, lowering the oxygen-carrying capacity of the blood. (1)

The most common and severe genotype is homozygous sickle cell anaemia (HbSS). Other genotypes are compound heterozygous forms in which HbS is combined with other haemoglobinopathies. The genotype spectrum includes amongst others sickle cell/haemoglobin C (HbSC), sickle cell/β^0 thalassemia (HbSβ^0) and sickle cell/β^+ thalassemia (HbSβ^+). When only one parent passes on the defective gene, the child will be a carrier and will have the sickle cell trait (instead of SCD). Most persons with sickle cell trait do not develop symptoms. (1)

SCD is characterised by the acute and unpredictable occurrence of vaso-occlusive crises (VOC). VOC occur when the microcirculation is obstructed by sickled RBC, causing ischemic injury to the organ supplied and resultant severe pain. Any organ can be affected, including the bones, lungs (acute chest syndrome, ACS), brain (stroke), finger/toes (dactylitis), spleen, liver, kidneys, penis (priapism) and joints. Triggers for VOC vary and can include inflammation, cold, stress, increased viscosity, decreased flow, haemolysis, or adhesion to endothelial cells, platelets and other inflammatory markers. (2)

1.2 Current treatment options

The only licensed treatment that is currently available for the prevention of VOCs is hydroxyurea or hydroxycarbamide (hereafter abbreviated as HU/HC). HU/HC showed to lower the frequency of VOCs by almost 50%. (3) Since the 80s HU/HC has been used off-label, but more recently different oral dosage forms have been registered in Europe (Siklos® tablets in 2007 (4); Xromi® oral solution in 2018 (5)).[1]

Not all patients demonstrate a clinical response to appropriate doses and duration of HU/HC therapy and develop cytopenia or other toxicities. In addition, also with appropriate HU/HC therapy VOCs can still occur. Finally, in some European countries registered HU/HC products are not reimbursed. For those patients that do not tolerate HU/HC, still experience VOCs despite HU/HC treatment, or do not have access to HU/HC, best supportive care is the only available treatment option. Best supportive care includes pain management (non-steroidal anti-inflammatory drugs, opioids and other analgesics) and other supportive care, such as (intravenous) hydration, oxygen therapy and/or blood transfusions. (6-8)

1 European guidelines on sickle cell disease management recommend HU/HC for adults who have 3 or more VOCs in a 12-month period, a history of severe/recurrent ACS or have pain or severe symptomatic anaemia that interferes with quality of life (QoL) or activities of daily living (ADL).

1.3 Crizanlizumab (Adakveo®)

This project plan focuses on the innovative pharmaceutical agent crizanlizumab (Adakveo®). The anticipated indication of crizanlizumab is as follows: crizanlizumab is a humanised, anti-P-selectin monoclonal antibody. Binding P-selectin on the surface of activated endothelium and platelets has been shown to effectively inhibit interactions between endothelial cells, platelets, RBC, sickled RBC, and leukocytes, thereby preventing (recurrent) vaso-occlusion. (9)

A conditional marketing authorisation application has been granted by the EMA for crizanlizumab for the prevention of recurrent VOC in SCD patients aged 16 years and older. The licensed indication states that crizanlizumab can be given as an add-on therapy to HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. Orphan designation was also granted by the EMA for humanised monoclonal antibody against P-selectin for the treatment of SCD in August 2012 (EU/3/12/1034).

2 RESEARCH QUESTION AND SCOPE

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

The following table provides the scope identified for the assessment of crizanlizumab.

Table 2-1: Assessment scope: relevant PICO(s) identified for the planned assessment

Description	Assessment scope
PICO	
Population	Crizanlizumab is indicated for the prevention of recurrent vaso-occlusive crises in sickle cell disease patients aged 16 years and over
Intervention	Crizanlizumab (in addition to standard care, including HU/HC and/or best supportive care)
Comparison	1. HU/HC plus best supportive care 2. best supportive care (if HU/HC is inappropriate or inadequate)
Outcomes	<u>Efficacy</u> ▪ Mortality * ▪ Annualized rate of VOCs leading to a health care visit or hospitalization * ▪ Time to first VOC * ▪ Percentage VOC event free * ▪ Health-related QoL * ▪ Annualized rate of days hospitalized * <u>Safety</u> ▪ Overall adverse events ▪ Treatment-related severe adverse events * ▪ Discontinuations due to treatment-related adverse events * ▪ Fatal adverse events *

Outcomes with an asterisk (*) were directly or indirectly mentioned by patient organisations to be of particular importance for patients with sickle cell disease.

3 METHODS

The EUnetHTA Guidelines, 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.

3.2 Information retrieval

The assessment will be based on a submission dossier submitted 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(s). 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. 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 results of these searches will be reported in the assessment.

If the evidence provided in the submission dossier is incomplete it will not be supplemented by own searches and 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 PICO 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 should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials (10) and non-randomised studies on interventions (11). The risk of bias of the results of each included study should be described separately for each patient-relevant outcome. For this purpose, risk of bias should be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high for an outcome, this should 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 (12)

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 0) 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 categorised. 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 (12). The indirect comparisons relevant for the research questions (see Section 0) 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 asks 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 are 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' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated.

The open call of crizanlizumab was online from 27th of September, 2019 until 21st of February, 2020. Two patient organisations completed the survey: the French Federation for Sickle Cell Disease and Thalassemia (France) and Sickle Cell and Thalassaemia Ireland (Republic of Ireland). The information gathered from the open call was used to inform the scope of this assessment and in particular the outcomes to be considered. In the PICO in Table 2-1, the outcomes related to issues particularly emphasised by the patient organisations are indicated with an asterisk (*). The vast majority of the outcomes were directly or indirectly mentioned by the patient organisations ensuring the clinical relevance of the outcomes used in the current assessment.

4 PROJECT ORGANISATION

4.1 Participants

Table 4-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Zorginstituut Nederland [ZIN]	Author	Netherlands	• Develop first draft and final version of EUnetHTA project plan with co-author • Initial literature search (including national/European guidelines) • Carry out the assessment: relative effectiveness (EFF) and safety (SAF) domains; support co-author in current treatment (CUR) and technical (TEC) domains • Send “draft versions” to reviewers, compile feedback from reviewers and perform changes according to reviewers comments • Prepare the final assessment including a final summary of the assessment • Answer external questions together with co-author • Responsible for final quality assurance
2.	Spanish Agency of Medicine and Sanitary Products [AEMPS]	Co-Author	Spain	• Develop first draft and final version of EUnetHTA project plan with 1st author • Support authors in literature search (including national/ European guidelines) • Responsible for supporting the authors in all project phases • Carry out the assessment: CUR and TEC Domains; support authors in EFF and SAF Domains. Support authors in Summary, Method, EFF/SAF and Discussion sections • Answer external questions together with 1st author • Check and approve all steps
3.	Zorginstituut Nederland [ZIN]	Information specialist	Netherlands	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
4.	• EUnetHTA Statistical Specialist Network • Zorginstituut Nederland [ZIN]	Statistical specialist	• Not applicable • Netherlands	Expert review of statistical analyses presented in submission dossier, statistical support for authors if needed
5.	French National Authority for Health [HAS]	Dedicated Reviewer	France	
6.	National Institute for Health and	Dedicated Reviewer	UK	

	Care Excellence Level [NICE]			
7.	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia [JAZMP]	Dedicated Reviewer	Slovenia	
Contributors				
8.	NA	External expert		Multiple clinical experts have been contacted, but all had conflicts of interest and therefore were not allowed to participate
9.	French Federation for Sickle Cell Disease and Thalassemia; Sickle Cell and Thalassaemia Ireland	Patient organisations		Completed the EUnetHTA open call in order to inform the scope of the assessment.
10.	TBD	Medical Editor		Responsible for the medical editing of the report
11.	Zorginstituut Nederland [ZIN]	Project Manager	Netherlands [NL]	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 4-2: Project stakeholders

Organisation	Role in the project
Novartis	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	**13-06-2019**	**21-10-2020**
Letter of Intent received	13-06-2019	
Scoping phase	**27-12-2019**	**24-07-2020**
Scoping PICO and development of first draft Project Plan	27-09-2019	11-11-2019
PICO survey – request relevant PICO from Member States	07-10-2019	18-10-2019
Adapt draft Project Plan based on PICO survey	29-10-2019	11-11-2019
Open call for patient input	27-09-2019	21-02-2020
Review of first draft Project Plan	12-11-2019	21-11-2019
Development of second draft Project Plan & answers to DR comments	22-11-2019	09-12-2019
Receive scoping F2F meeting documents from pMAH	11-02-2020	
Pre-scoping e-meeting with the assessment team	02-03-2020	
Share discussion topics for Scoping F2F Meeting	24-03-2020	
Scoping F2F meeting with manufacturer	31-03-2020	
Share action points from F2F meeting with manufacturer	07-04-2020	
(pre-)Assessment phase	**20-06-2020**	**24-07-2020**
Receive Submission Dossier from pMAH	19-06-2020	
Check formal completeness of Submission Dossier	20-06-2020	29-06-2020
Receive missing items and comments on the requests from the formal completeness check from pMAH	04-07-2020	
Start writing Assessment (background, methods)	30-06-2020	23-07-2020
CHMP opinion	24-07-2020	
Finalize Project Plan	27-07-2020	
Optional: Grace period to revise Submission Dossier by pMAH (based on CHMP opinion)	Not applicable	
Assessment phase	**23-07-2020**	**21-10-2020**
Writing first draft Joint Assessment	23-07-2020	21-08-2020
Review by DRs (and if applicable include experts)	24-08-2020	02-09-2020
Writing second draft Joint Assessment	04-09-2020	05-10-2020
Medical Editing	05-10-2020	09-10-2020
Fact Check by pMAH (parallel with medical editing)	05-10-2020	09-10-2020
Final Assessment + response Fact Check	19-10-2020	
Expected EPAR	12-10-2020	
Publication final version of rapid assessment	20-10-2020	21-10-2020

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