MIDOSTAURIN WITH STANDARD CHEMOTHERAPY IN FLT3 POSITIVE ACUTE MYELOID LEUKAEMIA

Project ID: PTJA01

Project description and planning

Authors: Finnish Medicines Agency
Co-authors: Norwegian Medicines Agency

Contents

A. VERSION LOG

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	03/03/17	FIMEA, NOMA	1st version (draft)	
V2	11/04/17	FIMEA, NOMA	2nd version (draft)	
V3	28/06/17	FIMEA, NOMA	3rd version (final)	

B. PROJECT PLAN

1.0 PARTICIPANTS

All individuals actively participating in the project.

Table 1. Project participants

#	Agency	Role in the project	Country	Distribution of work
1.	FIMEA	Author(s)	Finland	EFF, SAF
2.	NOMA	Co-Author(s)	Norway	CUR, TEC
3.	AEMPS	Reviewer	Spain	
4.	ZIN	Reviewer	Netherlands	
5.	TLV	Reviewer	Sweden	
6.	NICE	Reviewer	UK	
7.	HAS	Reviewer	France	
8.	IQWiG	Reviewer	Germany	Information retrieval
9.	SESCS	Observer	Spain	
10.	SU	Observer	Hungary	
11.	SUKL	Observer	Czech Republic	
12.	EOPYY	Observer	Greece	
13.	Dr. Baron, chairman of leukemia group of EORTC	External expert	Belgium	
14.	Dr. G.A. Huls, UMCG	External expert	Netherlands	
15.	TBD	Editor/Medical writer		
16.	Zorginstituut Nederland [ZIN]	Project coordinator	Netherlands	Coordination between involved parties throughout the assessment duration

1.1 PROJECT STAKEHOLDERS

Please describe/list project stakeholders

Table 2. Project stakeholders

Organisation	Role
Novartis Oncology Novartis Farma S.p.A.	*Marketing authorisation holder*

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this assessment report is to produce joint assessments on pharmaceuticals, that are fit for purpose, of high quality and of timely availability. In addition, the implementation of the jointly produced assessment in the national/regional practice will be facilitated.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	Indicator (and target)
1.	To produce joint assessments on pharmaceuticals, that are fit for purpose, of high quality and of timely availability	Production of 1 relative effectiveness assessment (REA).
2.	To apply these collaboratively produced rapid assessments into local (e.g. regional or national) context	Production of ≥ 2 national/local reports based on the REA.

This rapid assessment addresses the research question whether midostaurin in combination with standard induction and consolidation chemotherapy followed by single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive is more effective and/or safer than established alternative treatment options.

Table 3. Project Scope: PICO (please see HTA Core Model for Rapid REA of pharmaceuticals)

Description	Project scope
Population	Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive. ICD-10: C92.0 *Mesh-terms: Leukemia, Myeloid, Acute* *Tree Number(s): C04.557.337.539.275* *MeSH Unique ID: D015470*
Intervention	*There are three parts to the intervention: 1) induction therapy, 2) consolidation therapy and 3) continuation therapy. Eligible patients may receive SCT.* ***1) Induction Therapy:*** •*cytarabine 200 mg/m^2/day intravenously on days 1-7* •*daunorubicin 60 mg/m^2/day by intravenously on days 1-3* •*midostaurin 50 mg (two 25 mg capsules) twice a day orally on days 8-21* ***2) Consolidation (Four Remission Consolidation Cycles):*** •*high dose cytarabine 3g/m^2 every 12 hours on days 1, 3 and 5.* •*midostaurin 50 mg (two 25 mg capsules) twice a day by mouth on days 8-21* •*Dexamethasone 0.1% or other corticosteroid ophthalmic solution 2 drops to each eye once daily to begin 6-12 hours prior to the initiation of the cytarabine infusion and to continue for at least 24 hours after the last cytarabine dose.* ***3) Continuation Therapy:*** •*midostaurin 50 mg (two 25 mg capsules) orally twice a day for 28 days. Each cycle will be 28 days in length. Continuation therapy will continue until relapse or for 12 cycles maximum.* ***Note:** In clinical practice, variations may occur in the induction and consolidation therapy. For example, idarubicin may replace daunorubicin as an anthracycline, dose of cytarabine may vary both in the induction and consolidation therapy. Depending on line of the induction and consolidation therapy (i.e. first induction, second induction etc.) variations may occur and mitoxantrone may be added in second induction or third consolidation.* ***MeSH terms:** Midostaurin (MeSH Unique ID: C059539)*
Comparison	•*standard induction and consolidation chemotherapy (see above). Eligible patients may*

	receive SCT. • *standard induction and consolidation chemotherapy, except daunorubicin 90 mg/m^2/day (instead of 60 mg/m^2/day) is used in induction* • *azacitidine (for patients for whom stem cell transplant is not possible)* *Azacitidine is used for the treatment of adults with AML (under certain conditions), if they cannot have haematopoietic stem cell transplantation.* ***MeSH terms:*** *Azacitidine (MeSH Unique ID: D001374)*
Outcomes	***Overall survival (OS)*** ***Overall survival (OS)****, censoring patients who receive a stem cell transplant at the time of the transplant* ***Event-free survival (EFS)*** *- defined as the time from randomization until the earliest qualifying event, including: failure to obtain a CR on or before 60 days of initiation of protocol therapy; relapse; or death from any cause* ***Disease Free survival (DFS)*** *- defined as the time from documentation of first CR at any time to the first of relapse or death from any cause in patients who achieved a CR.* ***Complete Remission Rate (CR)*** *- Percentage of patients who achieved a complete response (CR). CR is defined as normalization of blood counts and a marrow showing less than 5% blasts occurring on or before day 60.* ***Cumulative incidence of relapse (CIR)*** *– percentage of patients who relapsed (a marrow showing more than 5% blasts) after receiving CR. CIR is measured at 12 months.* ***Proportion of patients who discontinued the treatment*** *– percentage of patients who discontinued the treatment by reason for discontinuation (e.g. failure to achieve complete remission, relapse, adverse event, etc.)* ***Health-related quality of life (HRQL)*** *– generic and disease specific HRQL* ***Adverse events*** *- Any AEs (adverse events), Serious AEs (SAE), Grade ≥3 AEs, Discontinuation due to AE, Death as SAE, AE of special interest.* ***Note!*** *Additional outcomes may be considered based on data presented in the submission or CSR. These data are currently not available for the authors.*

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
The information retrieval will be based on the Manufacturer's submission file, which should be composed applying the submission template and PICO presented in Table 3.The search strategies for published literature should be described and justified by Manufacturer following EUnetHTA guideline "Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness", as applicable. Internal validity should be assessed using the Cochrane Risk of bias tool. Quality of evidence should be assessed in the submission using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). An overview of the different treatment alternatives (induction-consolidation) across Europe should be also provided including discussion on how these differences could potentially influence the effect of midostaurin. Dedicated reviewers and clinical experts are specifically asked to comment this on the point of view of local practices during the assessment. In the submission, meta-analysis should be used for evidence synthesis if possible. Indirect comparisons should be utilized when direct evidence is not available or the choice of not including indirect comparisons should be justified. Indirect comparisons, in case applied, should be conducted according to EUnetHTA methods guideline on direct and indirect comparisons. Relevant subgroup analyses should be presented in the submission file especially for the most important outcomes. Subgroups of special interest are FLT3 mutation status (TKD, ITD allelic ratio) and SCT status. Furthermore, subgroup analyses based on genetic abnormalities should be explored. Especially the effect of NPM1 in combination with FLT3 status should be analysed. Authors will carry out a review of the evidence provided by manufacturer. Literature searches included in the Manufacturer's submission file will be checked for completeness against published literature and EMA and FDA web pages/databases by the authors. If there are major flaws in the bibliographic database search conducted by the manufacturer, then additional searches in bibliographic databases will be conducted. The results will be reported according to the Assessment Template for rapid REAs of pharmaceuticals.

Table 4b. Preliminary Evidence

Preliminary evidence table Please provide an overview of the most relevant studies included
RATIFY (CALGB 10603)
e.g. Clinical Study Report
Outcomes
Efficacy
Overall survival (OS)

Event-free survival (EFS)
Overall survival (OS), censoring participants who receive a stem cell transplant at the time of the transplant
Disease Free Survival (DFS)
Complete Response (CR)
Relapse rate
Health-related quality of life
Additional outcomes may be considered based on data presented in the submission or CSR. These data are currently not available for the authors.
Safety
Any AEs (adverse events)
Serious AEs (SAE)
Grade ≥ 3 AEs
Discontinuation due to AE
Death as SAE
AEs of special interest

Selected assessment elements

Table 5 shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessments elements contained in the document "Model for Rapid Relative Effectiveness Assessment".

Table 5. Assessment elements and translating research questions

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Description and technical characteristics of technology				
B0001 Critical element	Features of the technology and comparators	What is the technology and the comparator(s)?	*Yes*	*What is midostaurin and the comparators?*
A0020 Critical element	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	*Yes*	*What are the approved indications of midostaurin?*
B0002 Critical element	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparators?	*Yes*	*What is the claimed benefit of midostaurin in relation to the comparators in acute myeloid leukaemia (AML)?*
B0003 *Optional element*	*Features of the technology*	*What is the phase of development and implementation of the technology and the comparator(s)?*	*Yes*	*What is the phase of development and implementation of midostaurin and the comparator(s)?*
B0004 *Optional element*	*Features of the technology*	*Who administers the technology and the comparators and in what context and level of care are they provided?*	*No*	
B0008 *Optional*	*Investments and tools required to*	*What kind of special premises are needed for the technology and the comparator (s)?*	*No*	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
element	*use the technology*			
B0009 *Optional element*	*Investments and tools required to use the technology*	*What supplies are needed for the technology and the comparator (s)?*	*No*	
A0021 *Optional element*	*Regulatory Status*	*What is the reimbursement status of the technology?*	*No*	
Health problem and current use of technology				
A0002 Critical element	Target Condition	What is the disease or health condition in the scope of this assessment?	*Yes*	*What is acute myeloid leukaemia and natural course of the disease? What is the impact of FL3 mutation on prognosis and treatment choice?*
A0003 *Optional element*	Target Condition	*What are the known risk factors for the condition?*	*Yes*	*What are the known risk factors for AML?*
A0004 *Optional element*	Target Condition	What is the natural course of the disease or health condition?	*Yes*	*What is the natural course of AML? (briefly)*
A0005 Critical	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	*Yes*	*What are the symptoms and the burden of the disease or health condition for the patient?*

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
element				
A0006 *Optional element*	Target Condition	*What is the burden of disease for society?*	*No*	
A0024 *Optional element*	Current Management of the Condition	*How is the disease or health condition currently diagnosed according to published guidelines and in practice?*	*Yes*	*How is AML currently diagnosed according to European published guidelines?*
A0025 Critical element	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	*Yes*	*How is newly diagnosed acute myeloid leukaemia currently managed in clinical practice?*
A0007 Critical element	Target Population	What is the target population in this assessment?	*Yes*	*What is the target population in this assessment?*
A0023 Critical element	Target Population	How many people belong to the target population?	*Yes*	*How many people belong to the target population?*
A0011 *Optional element*	Utilisation	*How much are the technologies utilised?*	*No*	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Clinical effectiveness				
D0001 Critical element	Mortality	What is the expected beneficial effect of the intervention on mortality?	*Yes*	*What is the expected effect of midostaurin on overall survival?* • *This issue will cover the following outcomes:* • *Overall survival (OS)* • *Overall survival, censoring participants who receive a stem cell transplant at the time of the transplant*
D0005 Critical element	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition or disease?	*No*	*This issue will be covered in D0006 and partly elsewhere in clinical effectiveness domain.*
D0006 Critical element	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	*Yes*	*What is the effect of midostaurin on disease progression, treatment response and relapse rate?* *This issue will cover the following outcomes:* • *Event-free survival (EFS)* • *Disease Free Survival (DFS)* • *Complete Response (CR)* • *Relapse rate*
D0011	*Function*	*What is the effect of the technology on patients' body functions?*	*No*	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Optional element				
D0016 *Optional element*	*Function*	*How does the use of technology affect activities of daily living?*	*No*	
D0012 Critical element	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	*Yes*	*What is the effect of midostaurin on generic health-related quality of life?*
D0013 Critical element	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	*Yes*	*What is the effect of midostaurin on disease-specific quality of life?*
D0017 *Optional element*	*Patient satisfaction*	*Was the use of the technology worthwhile?*	*No*	
Safety				
C0008 Critical element	Patient safety	How safe is the technology in relation to (the) comparator(s)?	*Yes*	*How safe is midostaurin in relation to the comparators?* *The following outcomes will be covered in this issue:* • *AEs (adverse events)*

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
				• *serious AEs (SAE)* • *discontinuation due to AE* • *death as SAE* • *AEs of special interest* • *Grade ≥ 3 AEs* *Dose and time dependencies of harms and patient groups that are most likely to be harmed will be covered under this issue.*
C0002 *Optional element*	*Patient safety*	*Are the harms related to dosage or frequency of applying the technology?*	*No*	
C0004 *Optional element*	*Patient safety*	*How does the frequency or severity of harms change over time or in different settings?*	*No*	
C0005 Critical element	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	*No*	*This issue will be covered in C0008.*
C0007 *Optional*	*Patient safety*	*Are the technology and comparator(s) associated with user-dependent harms?*	*No*	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
element				
B0010 *Optional element*	*Investments and tools required to use the technology*	*What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?*	*No*	

Checklist for potential ethical, organisational, social and legal aspects

The following checklist should be considered in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the medicine to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new medicine will lead to changes.
If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further. Examples are provided for clarification (for more details please see also Model for rapid REA).

Table 6. Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	No
Example: The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available.	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	No
Examples: The new medicine will replace a surgical intervention which may lead to excess capacity in relevant areas. The new intervention requires the establishment of specialised centres for administration	
3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	No
Example: A medicine which is widely used by persons with abuse problems and which colours the tongue blue, thus immediately identifying the user as such. Comparators do not have this property.	
4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No
Examples: The comparator for the new medicine is a pharmaceutical which is not licensed in the indication of concern, but widely in use.	

The comparator for the new pharmaceutical is a controlled, restricted substance, the new medicine is not.

Note: The assessment should not address patent-related issues.

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)
Please select the steps which are applicable for this assessment.

Table 7. Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**25-11-2016**	**07-11-2017**
Expression of interest of manufacturer	25-11-2016/	
Pilot's team building (including possible external experts)	30-11-2016	21-12-2016
Scoping phase duration	**15-12-2016**	**20-06-2017**
Receive the Draft Submission File from MAH	12-04-2017	
Draft Project Plan	31-01-2017	03-03-2017
Review Draft Project Plan by dedicated reviewers and experts	06-03-2017	13-03-2017
Feedback on draft submission file	13-04-2017	28-04-2017
Receive Final Submission File from MAH	31-07-2017	
Final Project Plan	15-05-2017	29-06-2017
Assessment phase duration	**31-07-2017**	**03-11-2017**
First draft of the pilot assessment	*04-08-2017*	*10-09-2017*
Review of the first draft of the pilot assessment by dedicated reviewers	11-09-2017	18-09-2017
Second draft of the pilot assessment	*19-09-2017*	*09-10-2017*
Editorial version of the second draft	09-10-2017	16-10-2017
Consultation of the editorial version of the pilot assessment by external experts and MAH	17-10-2017	24-10-2017
Final version of the pilot assessment	*25-10-2017*	*08-11-2017*

Final technical editing and publication	09-11-2017	10-11-2017
Local Reports (if applicable)		

5.2 MEETINGS

A face-to-face scoping meeting will be planned with the manufacturer, authors and co-authors (see table 8). In addition, several e-meetings or teleconferences may be scheduled by the REA team, if considered necessary (see table 8).

6.0 COMMUNICATION

Table 8. Communication

Communication Type	Description	Date (if known)	Format	Participants/ Distribution
Kick-off authoring team	Informal kick-off meeting in which procedures are explained to involved parties	12-01-2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
Kick-off MAH	Informal kick-off meeting in which procedures are explained to involved parties	12-2016	e-meeting	MAH, CT
Scoping	To discuss draft submission file and reach consensus on the scoping (draft project plan)	03-05-2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
	To discuss scoping and draft submission file with MAH	09-05-2017	Face-to-face meeting	MAH, author(s), co-author(s), CT
Final Project Plan with timelines	Information on timelines, scoping, methods and assessment elements	29-06-2017	E-mail	Review by DR. Distribution to MAH, WP4 members
First draft of the assessment	To be reviewed by DR	01-09-2017	E-mail	DR
	To discuss comments of DR and reach consensus on adaptations	TBD ~ 02-10-2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
Editorial version of the pilot assessment	To be consulted with MAH and external experts	11-10-2017	E-mail	MAH, external experts
	To discuss comments of MAH (optional)	[DD/MM/YYYY]	e-meeting	Author(s), co-author(s), (dedicated reviewers)

6.1 DISSEMINATION PLAN

The final rapid assessment will be distributed as laid-out in the Work Plan of WP4.

7.0 COLLABORATION WITH STAKEHOLDERS

Collaboration with Market Authorisation Holder or prospective Market Authorisation Holder

Manufacturers can indicate their willingness to participate by submitting an expression of interest. The draft REA submission file provided by the company applying for market authorisation is the basic documentation for a rapid assessment and (in most cases) is received by authors before the positive opinion of the CHMP. Therefore the company applying for market authorisation is asked to provide the scientific discussion section of the CHMP report.

There will be a face-to-face scoping meeting of author(s)/co-author(s)/coordinators with the manufacturer. Within one week after face-to-face scoping meeting authors will send their feedback on the draft submission file to the manufacturer. The final submission file from the company is expected not later than by further four weeks, during which time the authors finalise the project plan and plan the timelines.

In general, the consultation with the manufacturer includes the project plan (especially timelines) and the second draft of the pilot assessment. However, if necessary, it is possible to send queries to the manufacturer during the assessment phase.

Collaboration with other stakeholders

The project plan and the 2nd draft version of the assessment report will be reviewed by external experts. The input of patients is sought when developing the project plan.

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual pilot rapid assessment, some collaboration with other WPs is planned. WP7 [Implementation] will be informed in time of the project plan and timelines, in order to prepare activities to improve national uptake of the final report. Feedback on the WP4 REA process will be asked from the involved parties, this information will be discussed with WP6 [Quality Management] to improve the quality of the process and output.

9.0 RESOURCE PLANNING

9.1 HUMAN RESOURCES

Table 9. Human resources

Role	Total number of person days	Source	
		Staff of participating organisations	Subcontracting
Author	60 person days	60 person days	-
Co-Author	40 person days	40 person days	-
Reviewer	5 person days each	5 person days each	-
Editor/Medical writer	5 person days	-	5 person days

The individuals participating in the production of the assessment will be asked to collect actual person days invested through a timesheet template.

10.0 CONFLICT OF INTEREST MANAGEMENT

Conflicts of interest will be handled according to EUnetHTA JA3 Conflict of Interest Policy. As conflict of interest may be topic dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific assessment via the Declaration of interest and confidentiality undertaking (DOICU) form. Authors and reviewers who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.
If external experts are involved in WP4 a conflict of interest declaration will be collected from them regarding the topic. External experts who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.

12.0 EXPECTED OUTCOME(S)

Project outcome(s)
Joint assessments on pharmaceuticals, that are fit for purpose, of high quality and of timely availability have been produced. These assessments will have been translated into local reports by which redundancies have been reduced and therefore efficiency gains have been achieved.