Regorafenib indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previoulsy treated with sorafenib

Project ID: PTJA02

Project description and planning

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Co-authors: Portuguese Authority of Medicines and Health Products (INFARMED)

July 2017

Contents

A. VERSION LOG

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	04/04/2017	HAS/INFARMED	1st version (draft)	
V2	21/04/2017	HAS/INFARMED	2nd version (draft)	Feedback from the DR
V3	21/07/2017	HAS/INFARMED	3rd version (final)	

B. PROJECT PLAN

1.0 ORGANISATION OF THE WORK

1.1 PARTICIPANTS

Table 1. Project participants

#	Agency	Role in the project	Country	Distribution of work
1.	HAS	Author(s)	France	Methods and evidence included, EFF, SAF
2.	INFARMED	Co-Author(s)	Portugal	TEC, CUR
3.	AAZ	Reviewer	Croatia	
4.	SNHTA	Reviewer	Switzerland	
5.	FIMEA	Reviewer	Finland	
6.	LBI	Reviewer	Austria	
7.	OGYEI	Reviewer	Hungary	
8.	AETSA	Reviewer	Spain	
9.	EOF	Observer	Greece	
10.	EKAPTY	Observer	Greece	
11.	TBD	Editor/Medical writer		
12.	Zorginstituut Nederland [ZIN]	Project coordinator	Netherlands [NL]	Coordination between involved parties throughout the assessment duration

1.1 MILESTONES AND DELIVERABLE(S)

Please select the steps which are applicable for this assessment.

Table 2. Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**24/01/2017**	**04/12/2017**
Expression of interest of manufacturer	24/01/2017	NA
Pilot's team building (including possible external experts)	30/01/2017	15/02/2017
Scoping phase duration	27/02/2017	11/07/2017
Receive the Draft Submission File from MAH	27/02/2017	28/04/2017
Draft Project Plan	27/02/2017	03/04/2017
Review Draft Project Plan by dedicated reviewers and experts	04/04/2017	11/04/2017
Feedback on draft submission file	29/04/2017	29/05/2017
Receive Final Submission File from MAH	05/06/2017	31/07/2017
Final Project Plan	05/06/2017	21/07/2017
Assessment phase duration	01/09/2017	04/12/2017
First draft of the pilot assessment	03/07/2017	31/08/2017
Review of the first draft of the pilot assessment by dedicated reviewers	01/09/2017	11/09/2017
Second draft of the pilot assessment	11/09/2017	25/09/2017
Editorial version of the second draft	25/09/2017	02/10/2017
Consultation of the editorial version of the pilot assessment by external experts and MAH	25/09/2017	02/10/2017
Final version of the pilot assessment	02/10/2017	18/10/2017
Final technical editing and publication	19/10/2017	24/10/2017
Local Reports (if applicable)		

1.3 PROJECT STAKEHOLDERS

Table 3. Project stakeholders

Organisation	Role	Contact details
Bayer U.S. LLC Pharmaceuticals MACS TA Oncology	*Market authorisation holder*	*100 Bayer boulevard Whippany, NJ 07981 United States*

2.0 PROJECT 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 local (e.g. national or regional) report per REA.

This rapid assessment addresses the research question whether Regorafenib (Stivarga©) in combination with best supportive care in hepatocellular carcinoma in patients who have been previously treated with sorafenib is more effective and/or safer than placebo in combination with best supportive care.

3.0 PROJECT METHOD AND SCOPE

3.1 APPROACH AND METHOD

Table 4. Project approach and method

Project approach and method
The information retrieval will be based on the Manufacturer's submission file. Direct evidence included in the Manufacturer's submission file will be checked for completeness with a systematic literature research performed in medline(1) and against EMA and FDA web pages/databases. Details of standard of care and therapeutic strategy for will be provided by independent clinical experts and HCC guidelines from society for medical oncology (ESMO(2) and NCCN(3) notably). Dedicated reviewers are specifically asked to comment this on the point of view of local practices. Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines (4) (5) (6). The Cochrane Risk of bias tool will be used on study and outcome level. The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Relevant subgroup analyses will be assessed especially for the most important outcomes. Subgroups of special interest are those that might affect prognostic and treatment choice (aetiology of HCC notably). Conclusion on efficacy endpoints, within intend to treat and subgroups populations, will be drawn according to their level of evidence. Statistical plan and methods to control the rate of the overall type I error will be particularly

analysed.
Given the preliminary data available, meta-analysis for evidence synthesis or for indirect comparison is not expected for this assessment (only one pivotal phase III trial and absence of valid comparators at this stage of the disease). In case MAH provide a meta-analysis, it should be conducted according to EUnetHTA methods guideline on direct and indirect comparisons

3.2 PROJECT SCOPE

Table 5a. Preliminary Evidence

Preliminary evidence table Please provide an overview of the most relevant studies included
RESORCE study[7] (NCT01774344)
e.g. Clinical Study Report

Table 5b. Project Scope: PICO (please see HTA Core Model for Rapid REA of pharmaceuticals)

Description	**Project scope**	**Major comments**
Population	Patients with hepatocellular carcinoma (HCC) who have been previously been treated with sorafenib. ICD-10: C22.0 Mesh-terms: carcinoma, hepatocellular Tree number(s): C04.588.274.623.160 MeSH Unique ID: D006528	The population included in the RESORCE trial seems extremely selected. Thus, regorafenib might be recommended for a small proportion of patients with HCC.
Intervention	Regorafenib 160mg orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) in combination with best supportive care (or palliative care). Regorafenib can be administered until disease progression defined by mRECIST, clinical progression (defined as an ECOG performance score ≥3 or symptomatic deterioration, including increased liver function tests) or unacceptable toxicity'. The regorafenib treatment could be continued beyond progression if the investigator judges that the patient would benefit from continued treatment.	NA

Comparison	Placebo in combination with best supportive care (or palliative care).	Currently, there are no other comparators that would be considered in routine clinical practice at this stage of the disease. However, during the current assessment process other therapeutic options may be available
Outcomes	**Efficacy**: - Critical outcomes: overall survival and quality of life - Important outcomes : progression free survival **Safety**: - Any adverse event (AEs) - Serious AEs - grade≥3 AEs - grade 3 AEs - grade 4 AEs - grade 5 AEs - discontinuation due to AEs - AEs of special interest (important risk identified in the Risk Management Plan).	In light of the poor prognostic of patients with HCC, effect on mortality is the key element expected for establishing clinical effectiveness. Given the known safety profile of regorafenib in already marketed indications and the poor prognostic of patients with HCC, a particular attention will be paid to quality of life (statistical methodology and results). To a lesser extent, progression free survival will be also taken into account for this assessment.

Preparation of the assessment phase checklist

Critical element:

What is regorafenib and the comparator(s)?

For which indications has regorafenib received marketing authorisation or CE marking?

What is the claimed benefit of regorafenib in relation to the comparators?

What is the disease or health condition in the scope of this assessment?

What are the known risk factors for HCC? Are they likely to impact patients' prognostic or treatment choice?

What is the median survival of patients with HCC? What is the median survival of patients targeted in the claimed MA?

What are the symptoms and the burden of HCC for the patient, in the targeted population?

How is the disease or health condition currently managed according to published guidelines and in practice?

What is the target population in this assessment?

How many people belong to the target population?

What is the expected beneficial effect of regorafenib on mortality?

How does regorafenib affect symptoms and findings (severity, frequency) of the disease or health condition or disease?

How does regorafenib affect progression (or recurrence) of the disease or health condition?

What is the effect of regorafenib on generic health-related quality of life?

What is the effect of regorafenib on disease-specific quality of life?

How safe is regorafenib in relation to (the) comparator(s)?

What are the susceptible patient groups that are more likely to be harmed through the use of regorafenib for HCC treatement?

Optional element:

What is the phase of development and implementation of regorafenib and the comparator(s)?

What is the reimbursement status of regorafenib?

What is the burden of HCC for society in terms of prevalence, incidence, mortality and costs, in the defined population?

What is the effect of regorafenib on patients' body functions?

How does the use of regorafenib affect activities of daily living?

Was the use of the technology worthwhile (according to patients opinion)?

How does the frequency or severity of harms change over time or in different settings?

Optional other dimensions (potential ethical, organisational, social and legal aspects)

NA for this REA

5.0 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	28/02/2017	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	09/02/2017	e-meeting	MAH, CT
Scoping	To discuss draft submission file and reach consensus on the scoping (draft project plan)	14/05/2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
	To discuss scoping and draft submission file with MAH	22/06/2017	Face-to-face meeting	MAH, author(s), co-author(s), CT
Feedback on draft submission file	To point out the requirements for the final submission file by MAH	28/06/2017	E-mail	MAH
Final Project Plan with timelines	Information on timelines, scoping, methods and assessment elements	21/07/2017	E-mail	Review by DR. Distribution to MAH, WP4 members
First draft of the pilot assessment	To be reviewed by DR	01/09//2017	E-mail	DR
	To discuss comments of DR and reach consensus on adaptations	TBD ~11/10/2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
Editorial version of the pilot assessment	To be consulted with MAH and external experts	25/9/2017	E-mail	MAH, external experts
	To discuss comments of MAH (optional)	TBD if necessary	e-meeting	Author(s), co-author(s), (dedicated reviewers)

5.1 DISSEMINATION PLAN

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

6.0 COLLABORATION WITH STAKEHOLDERS

Collaboration with Market Authorisation Holder or prospective Market Authorisation Holder

Bayer indicated their willingness to participate by submitting an expression of interest. The draft REA submission file provided by Bayer applying for market authorisation is the basic documentation for a rapid assessment and (in most cases) is received by HAS/INFARMED before the positive opinion of the CHMP. Therefore Bayer 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 HAS/INFARMED and ZIN with Bayer. Within one week after face-to-face scoping meeting HAS/INFARMED will send their feedback on the draft submission file to the Bayer. The final submission file from Bayer is expected not later than by further four weeks, during which time HAS/INFARMED 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 Bayer during the assessment phase.

Collaboration with other stakeholders

TBD

7.0 COLLABORATION WITH EUnetHTA WPs

For the individual 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.

8.0 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.

C. REFERENCES

1. EUnetHTA guidelines. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness

2. Verslype C, Rosmorduc O, Rougier P, ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2012; 23 Suppl 7:vii41-48.

3. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. V 2.2016

4. EUnetHTA guidelines. Levels of evidence. Internal validy of randomised controlled trials.

5. EUnetHTA guidelines. Comparators & Comparisons Direct and indirect comparisons

6. EUnetHTA guidelines. Endpoints used for relative effectiveness assessment: clinical endpoints.

7. Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 389(10064): 56-66.