Benefit-risk methodology project: update on work package 5: effects table pilot (phase I).

Report
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Benefit-risk methodology project

Update on work package 5: Effects Table pilot (Phase I)

1. Background

The aim of the European Medicines Agency (EMA) Benefit-Risk Methodology Project is to enhance the transparency of the benefit-risk decision-making process, and facilitate the communication of the rationale for each decision, both within the regulatory system and to the public. The project consists of five consecutive work packages[1]. The first four work packages formed the research phase of the project, and the fifth work package, currently ongoing, is intended as initial implementation and training. One of the recommendations of Work package 4 report[2] is the use of the Effects Table (ET) as a tool to summarise the key benefits and risks, and supplement the benefit-risk section of the CHMP[3] assessment report by presenting a compact and consistent display of the salient data and uncertainties that are drivers of the decision (Annex 1).

2. First pilot

After an initial period of testing, the CHMP agreed in November 2012 to initiate a five-month pilot of the ET (Annex 1). The pilot was agreed to last from January to May 2013 involving ongoing procedures for initial market authorisation. The rapporteur of each product was responsible for preparing the ET, and the project team provided support and guidance as necessary. In total, nine products were included in the pilot, four at Day 120 and five at Day 180 of the assessment process. All the tables were completed by the rapporteur/assessors on time with minimum support from the project team. Each ET was circulated by the rapporteur to the CHMP as a separate document complementing either the Day 120 or the Day 180 Assessment Report. A short feedback questionnaire was sent to the participating rapporteurs. The feedback collected presented, on average, a positive view on the use of the table as an aid in communicating the benefit-risk balance. It was noted that the table is a useful display of the key issues that can improve the transparency of the benefit-risk assessment, and support the communication with the other committees and the public. It was also noted that the ET should form an integral part of the benefit-risk section and be compiled early in the assessment process. Consideration should be given on improving the presentation of data from multiple trials and

[1] European Medicines Agency, Benefit-Risk Methodology Project. 2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109477.pdf.
[2] European Medicines Agency, Work Package 4 Report: Benefit-risk tools and processes 2012, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf.
[3] EMA's Committee for Medicinal Products for Human Use

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on the support that might be required from EMA for the finalisation of an ET. Following completion of this initial phase, the CHMP agreed to initiate a wider pilot of the ET (Annex 1), taking into consideration the feedback received.

Currently, there is no requirement to include an ET or any other framework or methodology into a Market Authorisation Application (MAA). The project's Steering Group has noted a number of cases of benefit-risk methods submitted by companies, either in the context of a Scientific Advice procedure or initial MAA. If this is considered useful, applicant companies are encouraged to include any framework or methodology in their applications, in addition to the conventional documentation, in order to gain more experience with such approaches. Additionally, questions on such methodologies can be addressed in the context of a Scientific Advice procedure.

3. Next steps

The CHMP agreed to initiate a phase II pilot of the ET. The main points are outlined below.

- Update the template/guidance of the ET based on the feedback received.
- Integrate the ET within the benefit-risk section of the assessment report.
- Pilot the ET on initial applications of new active substances starting from September to December 2013. The aim is to include at least ten products in this phase.
- Both Rapporteur and Co-rapporteur will prepare an ET that will be included in the Day 80 assessment reports. The tables will be updated throughout the procedure until the Day 210.
- Training and support will be provided by the project team and the Steering Group.
- The CHMP will have an interim evaluation of this pilot phase at mid-2014.

Annex 1 - Hypothetical example of an Effects Table

Table 1. Effects Table for **vandetanib** / Based on the EPAR EMEA/H/C/002315 published on 02/03/2012

	Effect	Short Description	Unit	Placebo	Vandetanib	Uncertainties / Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Mo	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Abbreviations: PFS, progression-free survival; ORR objective response rate; Mo, months; OS, overall survival; RET, “rearranged during transfection” gene, see text.