Outcomes of recent EMA/CHMP benefit-risk project (EPAR)

Current progress and future steps

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March 2008 CHMP: Reflection paper on benefit-risk assessment methods with two main recommendations:

1. Revise the benefit-risk balance section of the CHMP Assessment Report template

2. Research methodologies of benefit-risk balance
   - Involve experts, assessors, and specialists in Decision Theory
   - Improve consistency, transparency and communication of B/R
   - Switch from “implicit” to “explicit” decision making
5 Working Packages (WP)

1. Description of current practice
2. Applicability of current tools and methods
3. Field tests of tools and methods
4. Development of tools and methods for B/R
5. Pilot / Development of a training module
Development of tools/methods for B/R (WP4)

Integrated the results from the field tests to a methodology that can accommodate the needs of the various NCAs and the CHMP.

- The PrOACT-URL framework
- Two main tools
  - Effects table (qualitative): *General implementation in templates?*
  - MCDA based approach (quantitative): *In what specific situations?*
- Complexity of our process: *Where and when?*
The PrOACT-URL framework

⇒ A qualitative framework for structured decision making

1. Problem - Determine the nature of the problem and its context
2. Objectives - Establish objectives and identify criteria of favourable and unfavourable effects
3. Alternatives - Identify the options to be evaluated against the criteria
4. Consequences - Describe how the alternatives perform for each of the criteria
5. Trade-offs - Assess the balance among favourable and unfavourable effects
6. Uncertainty - Assess the uncertainty associated with the effects
7. Risk tolerance - Judge the relative importance of the decision maker’s risk attitude
8. Linked decisions - Consider the consistency of this decision with past/future decisions
## Effects Table (Hypothetical Example)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Short Description</th>
<th>Unit</th>
<th>Placebo</th>
<th>Vandetanib</th>
<th>Uncertainties/ Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (HR)</td>
<td>From randomization to progression or death (blinded independent review)</td>
<td>N/A</td>
<td>1</td>
<td>0.46</td>
<td>95% CI: (0.31, 0.69); Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>Weibull model</td>
<td>Mo</td>
<td>19.3</td>
<td>30.5</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>Proportion of complete or partial responders (&gt;=30% decrease unidimensional) RECIST</td>
<td>%</td>
<td>13</td>
<td>45</td>
<td>Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?</td>
</tr>
<tr>
<td><strong>Unfavourable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea Grade 3-4</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; Life-threatening</td>
<td>%</td>
<td>2.0</td>
<td>10.8</td>
<td>Duration of follow up in the pivotal study is short vs. the need for long duration of treatment.</td>
</tr>
<tr>
<td>QTc related events Grade 3-4</td>
<td>QTc &gt;0.50 second; life threatening; Torsade de pointes</td>
<td>%</td>
<td>1.0</td>
<td>13.4</td>
<td>Risk of developing further major cardiac SAEs including Torsades de pointes?</td>
</tr>
<tr>
<td>Infections Grade 3-4</td>
<td>IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening</td>
<td>%</td>
<td>36.4</td>
<td>49.8</td>
<td></td>
</tr>
</tbody>
</table>
Decision Analysis Modelling (MCDA)

Hypothetical example

5. Sensitivity Analysis:

6. Scenario Analysis...
   (explore various scores/weights)
Complexity of our process: Where and when?

Conclusions To Date

- **Effects Table**
  - Simple to build
  - Improve transparency, communication and consistency
  - Focus discussion on relevant issues

- **Decision Analysis Modelling (MCDA)**
  - Require more resources/effort to build model
  - Allow higher precision, sensitivity analysis
  - May be more relevant in borderline situations, many attributes, no established treatments
Next Steps

• Pilot and Training
  – Pilot and training (WP5) (Q2 2014)
    • Experiment effects table in Rapporteurs’ and CHMP assessment reports
  – Endorsement by CHMP (Q3 2014)

• B/R methodology as ongoing activity
  – Continue research for further improvement/development
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