PrOACT-URL (adapted for decision-making for benefit-risk assessment of medicines by the EMA BR Methodology Working Group)

| **STEP** | **DESCRIPTION** | **INFORMATION SOURCES** |
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| **Pr**OBLEM1. Determine the nature of the problem and its context. | 1a. The medicinal product (e.g., new or marketed chemical or biological entity, device, generic).1b. Indication(s) for use.1c. The therapeutic area and disease epidemiology1d. The unmet medical need, severity of condition, affected population, patients’ and physicians’ concerns, time frame for health outcomes. 1e. The decision problem (what is to be decided and by whom, e.g., industry, regulator, prescriber, patient) | “Acomplia: EPAR-Scientific Discussion” (on EMA website, under Acomplia, Assessment history, Initial Marketing authorisation documents). See 1. IntroductionIndication for weight loss, approved June 2006.Withdrawn January 2009. See “Assessment Report for Acomplia, Procedure No. EMEA/H/C/000666/A20/0012” Report No. EMEA/65105/2009(on website, under Acomplia, Assessment History, Changes since initial authorisation of medicine) |
| 2. Frame the problem. | 2a. Whether this is mainly a problem of uncertainty, or of multiple conflicting objectives, or some combination of the two, or something else (e.g., health states’ time progression).2b. The factors to be considered in solving the problem (e.g., study design, sources and adequacy of data, disease epidemiology, presence of alternative treatments). | 2a. Usually it is a mixture of favourable effect size, unfavourable effect seriousness and their uncertainties, but this may be more revealed in the EPAR than explicitly spelled out.2b. Ideally, only factors that make a difference to a decision need be included. |
| **O**BJECTIVES3. Establish objectives that indicate the overall purposes to be achieved.  | 3. The aim (e.g., to evaluate the benefit-risk balance, to determine what additional information is required, to assess change in the benefit-risk balance, to recommend restrictions). | 3. EPAR: 1. Introduction |
| 4. Identify criteria fora) favourable effectsb) unfavourable effects | 4. A full set of criteria covering the favourable and unfavourable effects (e.g., endpoints, relevant health states, clinical outcomes). An operational definition for each criterion along with a measurement scale with two points defined to encompass the range of performance of the alternatives (not just reported measures of central tendency, but also confidence intervals). Considerations of the clinical relevance of the criteria—some are of more concern to decision makers than others. | 4a. EPAR: 4. Clinical aspects especially Table 6 & Figure 14b. EPAR: Table 15 & associated textEstablishing two points on each measurement criterion facilitates scaling of the alternatives. Usually, data are reported only for the alternatives considered, but quantitative modelling requires definitions of two points on each measurement scale: e.g., lowest and highest practically-realisable measures. Quantitative weights assigned to the scales are based on considerations of relevance, which may not be documented, in which case the relevant stakeholders or key players can provide the information. |
| **A**LTERNATIVES5. Identify the options to be evaluated against the criteria. | 5a. Pre-approval: dosage, timing of treatment, drug vs. placebo and/or active comparator; the decision or recommendation required (e.g., approve/disapprove, restrict, withdraw).5b. Post-approval: do nothing, limit duration, restrict indication, suspend. | 5. As above, Step 1. Provide a clear definition of each option. |
| **C**ONSEQUENCES6. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects. | 6. The consequences separately for each alternative on each criterion (e.g., efficacy and safety effects that are clinically relevant, positive and negative health outcomes), summarised in an ‘Effects Table’ with alternatives in columns and criteria in rows. Qualitative and quantitative descriptions of the effects in each cell, including statistical summaries with confidence intervals, and references to source data, graphs and plots.  | 6. As above for Steps 3 and 4. It is rare to see all this information in one place. Usually, it is necessary to search for the information. If more than one study is reported, are decisions to be based on a single ‘best’ study or on combined data? Is a meta-analysis available? Can the effects table be populated with the results from several studies? Head-to-head comparisons are not necessarily needed for quantitative modelling. Report missing data. A quantitative model will require judgements of value functions, which express the clinical relevance of the data. |
| **T**RADE-OFFS7. Assess the balance between favourable and unfavourable effects. | 7. The judgement about the benefit-risk balance, and the rationale for the judgement.  | 7. EPAR: 6. Overall conclusions, benefit/risk assessment and recommendations. A quantitative model will also require judgements of weights associated with the criteria. |
| *At this point, only issues concerning the favourable and unfavourable effects, and their balance, have been considered. The next three steps are relevant in considering how the benefit-risk balance is affected by taking account of uncertainties.* |
| **U**NCERTAINTY8. Report the uncertainty associated with the favourable and unfavourable effects. | 8. The basis for and extent of uncertainty in addition to statistical probabilities (e.g., possible biases in the data, soundness and representativeness of the clinical trials, potential for unobserved adverse effects) | 8. EPAR: Tables 6 & Figure 1, and Table 15 for confidence intervals. Also “Discussion on clinical safety” under Table 16, and Table 17, and Overall conclusions (as at Step 7, above). Incidence data, reported at step 6 in the effects table, provide information relevant to the probabilities of realising the effects. |
| 9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty. | 9. The extent to which the benefit-risk balance in step 7 is reduced by considering all sources of uncertainty, to provide a benefit-risk balance, and the reasons for the reduction. | 9. No data for this. EPARs from late 2010, should provide information on this step. Judgement plays a key role in this step.A quantitative model will explore in sensitivity analyses and scenario analyses (or by explicitly incorporating probability distributions in the model) the effects on the overall benefit-risk balance of all sources of uncertainty. |
| **R**ISK TOLERANCE10. Judge the relative importance of the decision maker’s risk attitude for this product. | 10. Any considerations that could or should affect the decision maker’s attitude toward risk for this product (e.g., orphan drug status, special population, unmet medical need, risk management plan). | 10. No data for thisSome idea of the risk tolerance can be inferred from any report of step 9—how the favourable-unfavourable effects balance was affected by uncertainty. Another key role for judgement. |
| 11. Report how this affected the balance reported in step 9. | 11. The basis for the decision maker’s decision as to how tolerable the benefit-risk balance is judged to be (taking into account stakeholders’ views of risk?). | 11. See Step 1 document about the decision to withdraw Acomplia. In this case, it was new data obtained post-approval, as reported in sketchy form by EMEA/H/C/000666/A20/0012. |
| **L**INKED DECISIONS12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions. | 12. How this decision, and the value judgements and data on which it is based, might set a precedent or make similar decisions in the future easier or more difficult. | 12. See EPAR Conclusions.As all decisions are based not only on evidence, but also interpretations of that evidence that invoke value judgements and beliefs about uncertainty, decision makers may wish to reflect on whether those judgements and beliefs are consistent across similar past decisions, allow future changes and can be defended. |

Revision 5 (23 June 2011). Lawrence D. Phillips & the EMA BR Project Work Group members

*Disclaimer: This table is an adaptation of the original PrOACT-URL for PROTECT and is a working document. Please forward suggested additions and improvements derived from its use to* *lawrence.phillips@ema.europa.eu**.*

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