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Significant benefit of orphan drugs: concepts and future developments

Significant benefit is one of the criteria for orphan designation. It is defined in Regulation (EC) No 141/2000 as a “*clinically relevant advantage or a major contribution to patient care*”. The concept of significant benefit is unique to the EU orphan legislation, and does not exist in clinical pharmacology or in any other regulatory framework. The aim of the workshop was to discuss the assessment of significant benefit by the Committee for Orphan Medicinal Products (COMP) at time of orphan designation and marketing authorisation. The workshop included discussions on ways to communicate the grounds for significant benefit more explicitly and how to develop a systematic approach to its assessment.

The first part of the workshop reviewed the legal basis and the concept of significant benefit as it has been applied by the Committee for Orphan Medicinal Products (COMP) in more than 10 years of experience. The Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C 178/02) and the Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009) elaborate on the significant benefit justifications, provides general guidance and discuss data requirements for supporting significant benefit claims. Due to the early stage of development of most products the significant benefit at orphan designation is based on assumptions, supported by “proof of principle” evidence in relevant experimental studies or early clinical data.

Up to now 71 orphan medicinal products have received orphan designation and been authorised⁷, 75% of which required significant benefit. In a retrospective analysis conducted at EMA on the grounds for significant benefit of the authorised products, significant benefit was granted much more often based on a ‘clinically relevant advantage’ than on a ‘major contribution to patient care’. This reflects the fact that major contribution to patient care is based on “soft” endpoints (e.g. patients’ preference, compliance) which are usually not addressed in the pivotal clinical trials performed for the marketing authorisation application, or on self-evident advantages, the relevance of which might be difficult to establish.

Out of the designated authorised orphan products, 56% were authorised with a ‘normal’ marketing authorisation, 38% under exceptional circumstances and 6% received a conditional approval. While there is a possibility to provide additional data to confirm the benefit risk balance after marketing authorisation in the form of specific obligations in the conditional marketing authorisation, there is no



such thing as a 'conditional' significant benefit. TNo additional data can be submitted after marketing authorisation for this purpose, which may be a limitation in some cases.

At the time of marketing authorisation, the significant benefit should be based on evidence from clinical data confirming the assumptions and hypotheses provided at designation. Methodological issues around significant benefit can arise when the population size, in the condition as applied for, does not allow conducting randomised active control trials, or when the COMP assessment requires discussing significant benefit against a large number of comparators. Protocol assistance is a key tool for improving the chances of obtaining marketing authorisation, and maximising the possibilities of retaining the orphan designation, including discussing how to demonstrate significant benefit.

The new COMP assessment report on the maintenance of orphan criteria at marketing authorisation aims at increasing transparency on this procedure. The participants in the workshop stressed that initiatives towards a more complete publication of the COMP assessment would be welcome. Positive and negative decisions on the review of orphan designation at marketing authorisation are published on the EMA website since January 2010. The information on marketing authorisations is published in the European Public Assessment Report (EPAR), with a link to the specific COMP public summary opinion (PSO) on the review of orphan designation criteria.

WORKSHOP REPORT MAIN CONCLUSIONS

- The main conceptual grounds for significant benefit have been identified from the working experience of the COMP but there is the need for making them more explicit. Work should be done on a better definition and structure of the scientific justifications for significant benefit, including a review of the level and type of data requirements.
- As there are no procedures allowing post-marketing submission of data for significant benefit, strengthening the input on significant benefit at the time of protocol assistance/scientific advice appears to be a crucial step.
- There is the need for more comprehensive public information on the assessment of significant benefit, and in general more on the orphan criteria, particularly at time of marketing authorisation. It is necessary to provide clear, robust and well structured information on the scientific basis for assessment of significant benefit, which can be of use to any stakeholders with responsibilities on medicinal products after marketing authorisation.
- Further interaction and information exchange between the COMP and the CHMP on significant benefit are welcome in order to discuss and better define the data required for significant benefit, particularly regarding secondary endpoints in relation to major contribution to patient care, and different comparators.