BfArM

Bundesinstitut für Arzneimittel und Medizinprodukte

Regulators' Assessment for Marketing Authorization Decisions

The ultimate goal is the best possible patients' access to innovative anticancer products. A number of malignant diseases are considered as rare diseases for which orphan drug development is supported by various EU incentives. Innovative anticancer products and orphan medicinal products are in the mandatory scope of the centralized procedure at the European Medicines Agency (EMA). The European pharmaceutical legislation includes directives which have to be implemented nationally, e.g. via Arzneimittelgesetz (AMG) and directly binding regulations that need no national transformation. Based on internationally harmonized regulatory guidelines EMA's Committee for Medicinal Products for Human Use (CHMP) assesses the applications. The benefit-risk assessment addresses the efficacy in the clinical context of the condition and the relative efficacy from pivotal studies versus comparator.

The CHMP opinion of a positive benefit-risk-ratio is the basis for the decision on the marketing authorization by the European Commission.

The divergence of marketing authorization and reimbursement decisions may be conceived as contradictory by patients and public and may jeopardize patients' access to innovative medicines. EMA is pursuing the alignment of various stakeholders, including HTA bodies, industry and patients' representatives early during development.

At the time of marketing authorization, regulators' assessment is comprehensive. The basis for the assessment exceeds publicly available information and may include confidential or unpublished data for the innovative product and relevant comparator products. The decision on marketing authorization is based on the benefit risk ratio of the product. The assessment report describes frequency and importance of beneficial effects and the clinically relevance, the severity and frequency of adverse effects, and uncertainties of the data. A head-to-head comparison with a state of art treatment option is usually required for the pivotal studies of the application. Depending on the clinical setting and the comparator both a superiority design and a non-inferiority design may be acceptable. Decisions on marketing authorization based on studies without comparator arm but with indirect comparisons may be justified, e.g. if the comparator became available only after the pivotal studies had been started. Whereas clinical endpoints are the standard in the pivotal trials surrogate parameters may be acceptable if they are generally accepted to predict clinical outcome and/or outcome studies are not feasible prior to marketing authorization. In the context of oncology applications time-dependent endpoints, e.g. overall survival and often progression-free survival are considered as clinically relevant endpoints.

In addition to the full authorization in the standard procedure, conditional approval and approval under exceptional circumstance may be granted. Conditional approval may be used in cases of an unmet medical need and with a clearly positive preliminary benefit – risk assessment, but with the need for confirmation by more mature data or additional studies. Approval under exceptional circumstance may be used e.g. for very rare tumors when it is not possible to recruit a sufficiently large number of patients to conduct reasonably powered, randomised studies. These will frequently be orphan medicines (medicines for rare diseases). For orphan medicinal products, EMA's Committee for Orphan Medicinal Products (COMP) will explicitly confirm the significant benefit of the

new product after and - independently from - CHMP's positive opinion on the marketing authorization.

The scientific assessment for the marketing authorization is expected to be a useful basis for subsequent decisions by HTA bodies/payers. Their decisions, however, will need to address additional problems. For example, the regulatory assessment discusses the magnitude of beneficial effects usually based on the ITT population rather than responders and separately for different indications and patient populations. Regulators' assessment for marketing authorization cannot and must not predetermine reimbursement or prize decision. Regulators may, however, contribute their evidence-based scientific assessments to be used by HTA bodies and payers within their own assessments and decisions. A transparent and bidirectional communication between HTA bodies / payers and regulators may help to avoid mutually exclusive assessment results and promote public and patients' acceptance of decisions.