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Current Perspective

Therapeutic indications in oncology: Emerging features and regulatory dynamics

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ARTICLE INFO

Article history:
Received 18 November 2009
Accepted 24 November 2009
Available online 26 December 2009

Keywords:
Therapeutic indication
EMEA
Restriction of indication
Regulatory
Anticancer drugs
Extension of indication
Oncology

ABSTRACT

The regulatory route leading to the definition of therapeutic indications of new compounds as well as extensions of indication (EoI) of already approved ones is a challenging process. If new anticancer drugs reach the market with a lack of complete evidence, this usually leads regulators to request additional data, post approval commitments or restrictions in therapeutic indications.

This study aims at quantifying the time needed for anticancer drugs approved by the EMEA to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) significantly decrease from about 81 months in 1996 to 6 months in 2006. Twenty-four out of 43 approved anticancer medicines (about 56%) have only a single therapeutic indication, 12 of which were approved before 2005.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval (CI): 0.07–1.04). With regard to the type of EoI ($n = 60$), our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour, in 37% of cases the extension consisted in a switch of line within the same therapeutic indication. The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient population (7%).

The analysis of indication restrictions showed that in 20 cases out of 50 (40%) therapeutic indications were restricted by the Committee for Medicinal Products for Human Use (CHMP) during the assessment, with 60% of the restrictions occurring in 2006–2007.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.11.021

This study adds three main pieces of information: (i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments.

1. Background

Once a medicinal product is on the market, companies usually perform new clinical studies to extend therapeutic indications.[1] Providing data from new trials is a requirement for expanding the indications, contrarily to the past, when case series or other less robust methods were considered sufficient evidence for this purpose. New indications may also include new patient settings or a switch in the treatment line (e.g. from second to first line). The regulatory route leading to the definition of therapeutic indications of new compounds and extensions of indication (EoI) of already approved ones are challenging processes. This is particularly the case for oncology, where there are many unmet medical needs, and where new therapeutic opportunities are often immediately translated into clinical practice. This process is per definition complicated by the fact that new anticancer drugs reach the market with a lack of complete and sound evidence.[2–5] An uncertain benefit/risk profile of a drug is hard to review for regulators, which usually leads to the requests for additional data, post approval commitments or restrictions in therapeutic indications.[6,7] A restriction of therapeutic indications is a tool with an immediate effect, which aims at identifying the specific patient's population that may benefit most from the medicine. Restrictions may also fuel off-label prescribing instantly, and on the long run, slow down the availability of formally approved indications and the investments in therapeutic innovation in general.

A critical factor is timing of a positive (or negative) decision about an additional and new indication of a medicinal product. When the decision is made (too) fast, patients may be exposed to treatment on the basis of premature, weak or very uncertain data, asking for more and additional evidence to support a new indication. This study aims at quantifying the time needed for an anticancer drug to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

2. Methods

Information on regulatory steps leading to the definition of therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Report (EPAR), publicly available on the EMEA website (http://www.emea.europa.eu/htms/human/epar/eparintro.htm).

Documents were surveyed for new applications as well as for later extensions between January 1995, when the EMEA was set up, and December 2008. The analysis includes all the anticancer drugs with a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) through the so-called Centralised Procedure. As the interferon α-2b (INFα-2b) application was aimed at obtaining a European Marketing Authorisation (MA) after earlier authorisations had been granted at the national level, there was not sufficient information for its oncology indications and the drug was therefore excluded from the analysis. Palliative or supportive therapies (such as bisphosphonates, immunoglobulins and anti-emetics), hormone treatments, colony-stimulating factors, chemoprevention treatments, vaccines and generics were also excluded from the analysis.

For the purpose of this analysis, the following parameters were extracted: active compound, date of issue of the European MA, number of therapeutic indications, study characteristics (design, number of patients and primary end-point), indication requested (IR) by the applicant and indication approved (IA) by the CHMP. Only indications for which the IR was clearly stated in the EPAR were considered eligible for the analysis. Then, a comparison between IR and IA was performed in order to find possible restrictions. The analysis of the types of extensions of indication was performed considering the following pre-specified categories: (i) new tumour, (ii) tumour stage, (iii) new population and (iv) switch in the treatment line. We defined *a priori* two common data acquisition forms to be completed. FT and GT independently evaluated all the EPARs and filled the respective forms. The results were then cross-checked, leading to a joint document. In the case of disagreement, the final decision was taken through a consensus process reached following further discussion.

3. Results

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. Overall, 60 EoI were approved between 1995 and 2008. An increasing trend in EoI can be observed since 2002, with a median of 8 approved indications per year, while before 2002 only 5 out of 60 EoI (8.3%) were approved. In contrast, the rate of newly approved oncological products remains almost constant within the time frame 1995–2008 with an average of 3.3 per year. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) was also calculated, using the dates of European MA for each indication (Fig. 1).

A significant continuous decline of TtNE has been shown from 1995 up to 2008. For example, this means that for an anticancer medicine approved in 1996, about 81 months were necessary to have a new indication approved for the same drug. While for a product approved in 2006, the time needed was much shorter, i.e. 6 months.