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Early benefit assessment of new drugs in Germany – Results from 2011 to 2012

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ABSTRACT

Rising drug costs in Germany led to the Act on the Reform of the Market for Medicinal Products (AMNOG) in January 2011. For new drugs, pharmaceutical companies have to submit dossiers containing all available evidence to demonstrate an added benefit versus an appropriate comparator therapy. The Federal Joint Committee (G-BA), the main decision-making body of the statutory healthcare system, is responsible for the overall procedure of "early benefit assessment". The Institute for Quality and Efficiency in Health Care (IQWiG) largely conducts the dossier assessments, which inform decisions by the G-BA on added benefit and support price negotiations. Of the 25 dossiers (excluding orphan drugs) assessed until 31 December 2012, 14 contained sufficient data from randomized active-controlled trials investigating patient-relevant outcomes or at least acceptable surrogates; 11 contained insufficient data. The most common indications were oncology (6) and viral infections (4). For the 14 drugs assessed, the extent of added benefit was rated as minor, considerable, and non-quantifiable in 3, 8, and 2 cases; the remaining drug showed no added benefit. Despite some shortcomings, for the first time it has been possible in Germany to implement a systematic procedure for assessing new drugs at market entry, thus providing support for price negotiations and informed decision-making for patients, clinicians and policy makers.

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1. Background

The statutory health insurance (SHI) system covers about 90% of the population in Germany [1]. The main decision-making body of SHI is the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA), which is primarily responsible for reimbursement decisions [2]. The Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG), established in 2004, is Germany's main health technology assessment (HTA) agency within SHI [3,4]. Its primary responsibility is the production of HTA reports on the patient-relevant benefit of drugs and non-drug interventions. These reports inform decision-making by the G-BA.

Until 31 December 2010, the price of a new drug introduced into the German market was not regulated or negotiated by a health care or governmental body but solely set by the pharmaceutical industry. As a result, Germany generally pays higher drug prices than other European countries [5], and rising costs have led to the introduction of various cost-containment regulations. A major milestone, the Act on the Reform of the Market for Medicinal Products (*Gesetz zur Neuordnung des Arzneimittelmarktes* – AMNOG), came into effect on 1 January 2011 [6,7]. According to the German Federal Ministry of Health, AMNOG "aims to curb the spiralling expenditure for medicinal products by the statutory health insurance funds. It paves the way for fair competition and a stronger orientation to patients' well-being" and "creates a new balance between innovation and the affordability of medicines" [6]. However, the introduction of AMNOG aroused substantial opposition, largely

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from the pharmaceutical industry, which queried the feasibility of early benefit assessments regardless of the fact that this type of procedure has been established in other countries for several years. For instance, it was doubted whether randomized controlled trials could be available at the time of market entry to demonstrate a "therapy relevant added benefit" of a new drug versus an established comparator treatment [8]. These concerns related particularly to oncology drugs [9].

The German Social Code Book V (*Sozialgesetzbuch*, SGB V) regulates the statutory health care services and has been amended in accordance with AMNOG. The new § 35a SGB V regulates the assessment of the benefit of new drugs (i.e. of drugs with new active ingredients): as soon as a new drug enters the German market, the pharmaceutical company is required to provide evidence of its added benefit for patients compared with an appropriate comparator therapy (ACT), i.e. the current standard treatment, specified by the G-BA [10]. For this purpose, the company must submit a dossier containing a systematic review of the results of all published and unpublished clinical trials on the new drug. This approach aims to prevent the well-known effects of publication and outcome reporting bias [11,12]. In addition, the company has to provide an estimate of the number of patients who could benefit from the new drug as well as an estimate of the corresponding drug costs. The G-BA is responsible for the early benefit assessment and generally commissions IQWiG to assess the dossier and evaluate the probability and extent of added benefit [13], which are determined as described in Box 1.

The resulting assessment report by IQWiG is forwarded to the G-BA: this "dossier assessment" is published on the G-BA website together with the company's dossier and informs the G-BA's decision on added benefit. This decision, together with the estimated number of patients who may benefit from the new drug and the estimated drug costs, then form the basis for pricing negotiations between the SHI umbrella organization (*GKV-Spitzenverband*) and the pharmaceutical company. Exemptions from the above procedure apply to orphan drugs, which according to § 35a are classed as having an added benefit, provided their turnover is less than € 50 million per year [14]. However, the company responsible still has to submit a dossier, so that the extent of added benefit can be assessed by the G-BA and used as a basis for price negotiations. The results of benefit assessments of orphan drugs are not covered in this paper.

The aim of our paper is to provide an overview of the first results of the early benefit assessment of new drugs in Germany.

2. The first year with AMNOG

2.1. Analysis of dossier assessments

The first dossier assessment was published in October 2011. A German-language article by IQWiG published in October 2012 [15] presented results of dossier assessments published between October 2011 and June 2012. We extended the period to December 2012, and extracted the following information from the dossier assessments: number of dossiers assessed by IQWiG, number of dossiers containing sufficient data for assessment, types of drugs analysed, and results of the assessments of the extent of added benefit.

Box 1
Excursus – determination of the extent and probability of added benefit

On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of a new drug for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) "none of the first 3 categories applies" (i.e., no data available or conclusions 1–3 cannot be drawn from the available data), see [26]. The extent of added benefit or harm is graded into 6 categories: The categories of (1) major, (2) considerable, (3) minor or (4) non-quantifiable extent of added benefit are used if an added benefit is shown; in addition, (5) no added benefit, or (6) less benefit may apply), see Ref. [13].

The above categories for the extent of added benefit are defined verbally in the Regulation for Early Benefit Assessment of New Pharmaceuticals (*Arzneimittel-Nutzenbewertungsverordnung*) [27]. Based on the wording of the regulation, IQWiG has operationalized these categories by means of an algorithm that takes into account the relevance of the outcome (e.g. survival is weighted higher than a non-serious adverse event) and the magnitude of the treatment effect. Using this algorithm, in a first step IQWiG determines the extent and probability of added benefit of a new drug separately for each patient-relevant benefit and harm outcome. In a second step, these results are aggregated into an overall balancing of benefits and harms, resulting in a conclusion on the net added benefit in the IQWiG dossier assessments. The detailed approach is presented in the appendix to IQWiG's first dossier assessment, Ticagrelor [13] and in the current version of IQWiG's methods paper (Version 4.1: [26]).

IQWiG completed 27 dossier assessments by 31 December 2012. Two of these were on orphan drugs and are not considered further. Fourteen dossiers contained sufficient data for assessment (in all cases including evidence from active-controlled randomized trials); 11 contained insufficient data (Fig. 1).

The trials included in the 14 dossiers represented direct comparisons of the new drug and the ACT in at least one relevant group of patients, i.e. patients for whom the drug had been approved. All of these trials investigated patient-relevant outcomes (or at least acceptable surrogate outcomes, see below). The therapeutic indications most commonly investigated were cancer (n = 6), and viral infections such as HIV (n = 2) and hepatitis C (n = 2) (Table 1).

For 13 of the 14 new drugs, an added benefit was determined in at least one relevant patient group. No new drug was classified as showing a major added benefit; 13 showed either a hint, an indication or proof of a minor (n = 3), considerable (n = 8) or non-quantifiable (n = 2) added benefit.

All 6 dossiers on cancer drugs contained data on overall survival. However, health-related quality of life was only

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