G-BA conditional approvals in the AMNOG procedure: Impact on HTA outcomes and price

Justus Dehnen, Dennis Petry, Fabian Kruse, Jakob Bercher; CRA, Charles River Associates, Life Science Practice, Leopoldstr. 8, 80802 Munich, Germany

Introduction

Since AMNOG (Arzneimittelmarktneuordnungsgesetz) was introduced in 2011, pharmaceutical manufacturers are required to submit a benefit dossier for each innovative drug to the Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss). The benefit assessment results serve as the basis for subsequent price negotiations with the Head Association of the Statutory Health Insurance (GKV-Spitzenverband).

Orphan drugs receive an additional benefit by default, but may receive a nonquantifiable one due to limited availability of clinical evidence.

Where evidence is preliminary or insufficient, the G-BA may apply a time limit to a product's resolution, requiring the product to undergo another early benefit assessment after the expiration of the initial assessment.

In this study, we investigate the incidence of time-limited resolutions and the role of the orphan status and therapeutic area. We aim to better understand the reasoning driving time-limited assessment outcomes. Ultimately, we explore the impact of the final, updated benefit rating after the re-assessment on price.

Methodology

Using the G-BA website, we collected all time-limited G-BA resolutions since the introduction of AMNOG.. For each time-limited assessment, we tracked therapeutic area, orphan status, benefit rating, date of and reasons for re-evaluation, as well as first and final resolution dates.

We then compared the benefit assessment outcomes after the re-assessment of those drugs for all drugs with a finalised re-assessment until June 2018. To identify the impact of the updated benefit assessment outcomes, we collected the manufacturer selling price and negotiated rebates at launch, prior to re-evaluation, and after re-evaluation.

Discussion and conclusions

Time-limited assessments represent approximately 15% of all resolutions passed by the G-BA. The G-BA generally uses the possibility to limit the benefit assessments to a certain time frame to ensure all relevant evidence can be considered for the final benefit rating. Often (35% of all limited resolutions), the G-BA is following EMA in case of conditional EMA approval.

A time-limited rating does not necessarily lead to a less favourable assessment outcome initially. In fact, the distribution of additional benefit of time-limited resolutions seems to be in line with the distribution throughout all drugs that have gone through AMNOG (also considering the high share of orphan drugs among time-limited assessments, explaining the high prevalence of "unquantifiable"-ratings).

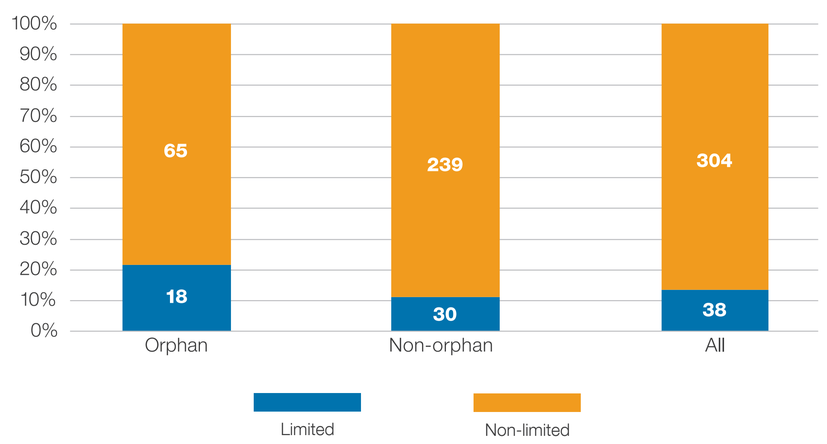
However, the probability of improving a drug's initial rating through the second assessment (after expiration of the first) is just as likely as the probability of worsening it (~40%).

This change in benefit level has an impact on the rebate, which will be renegotiated by manufacturer and GKV-SV after the second assessment. One would expect that a decrease in additional benefit would lead to an increase in rebate and vice versa.

While the sample size for this analysis is small (n=16), the comparison of change in rebate and change in benefit level shows that this expectation is true to some degree: a worsened rating (especially one where all added benefit is lost across subpopulations) is likely to lead to an increase in negotiated rebate (4/6 cases, one is unchanged), while an improved rating is more likely to lead to an increase in reimbursed price (3/7 cases, 3 are unchanged).

It is worth noting that some manufacturers use this mechanism to their advantage. One drug (Tagrisso) was not launched until it improved significantly in its re-assessment, while another (Stivarga) was taken off the market during price negotiations after its added benefit decreased significantly, most likely to prevent the publication of a high rebate.

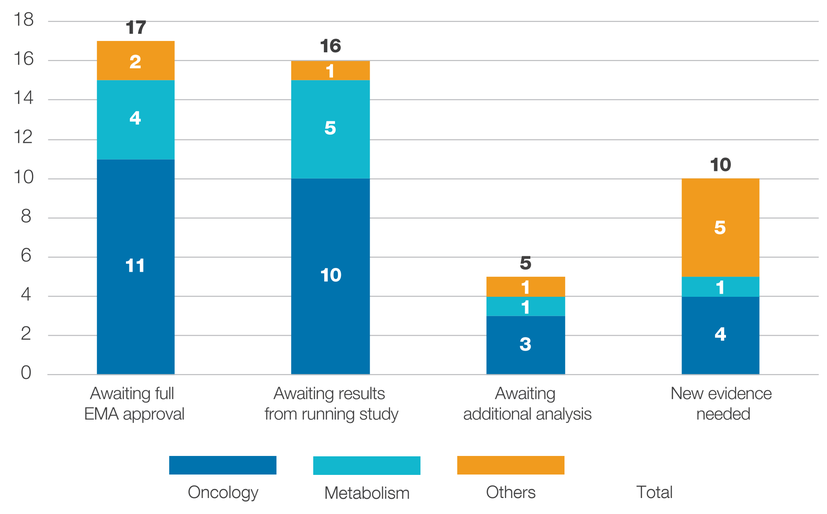
Figure 1: Impact of orphan status



Time-limited resolutions overview:

Considering all 353 concluded G-BA resolutions through mid-October 2018, 48 (14%) were given a date for re-evaluation of their benefit ratings. The incidence of time-limited resolutions for non-orphan drugs is only 13% (n=30/269), while 28% of orphan drugs (n=18/83) receive a time-limited resolution. This suggests that orphan drugs are at a higher risk of being subject to a time-limited assessment.

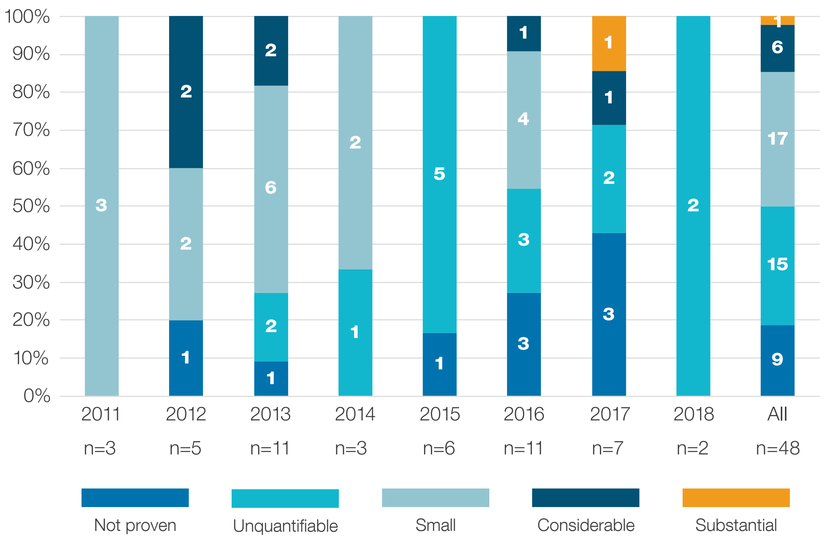
Figure 2: Reasons for limited resolutions



Reasons for limited resolutions by therapeutic area:

The reasons for the G-BA to apply a time limit to an assessment can be classified into four categories: (I) the drug received conditional EMA approval and additional data have to be presented (35%), (II) the G-BA requests to assess results from running studies before giving a final verdict (33%), (III) it wants to see specific analyses based on existing evidence (10%) or (IV) new evidence is required altogether (21%). This indicates that a substantial part of re-assessments can be managed with existing data or data that are already being generated. Most frequently, drugs in oncology or metabolic diseases receive a time-limited benefit rating, reflecting the high evidence requirements specifically in oncology.

Figure 3: Benefit ratings



Resulting benefit ratings from limited resolutions:

As laid out before, a time-limited benefit rating from the G-BA generally results from a lack of robust evidence, therefore one could expect low levels of additional benefit for products with a time-limited assessment. Indeed, many drugs with a time-limited assessment received a non-positive rating (counting an unquantifiable rating as non-positive, as automatically granted for orphan drugs).

Still, a surprisingly large share of products (around 50%) have reached a positive quantifiable rating (i.e., minor additional benefit or better), seven even received a high rating of "substantial" or "considerable". There has been no clear trend regarding the occurrence of limited resolutions over the years.

Figure 4: Change in benefit level vs. change in negotiated rebate

Legend:
Worsened significantly: No sub-population retained positive rating after re-assessment;
Worsened: While at least one sub-population retains a positive rating, the overall added benefit rating across all sub-populations has worsened;
Unchanged: No change in benefit assesment outcomes;
Improved: More sub-population benefit ratings improved than worsened;
Improved significantly: Initially no positively assessed sub-population, now at least one

For the pricing analysis, we assessed drugs that underwent their re-assessment process after expiration of the initial assessment results and received a new benefit rating (n=20), while disregarding those that left the market before a new rebate could be negotiated (n=4). We retrieved historical prices and rebates from LauerTaxe and compared the negotiated rebates prior to and after the drug's re-assessment by the G-BA.

We assumed causality (change in rebate triggered by re-assessment results), as all changes in rebate occurred between one and eight months after a new rating had been given. Our results show a correlation between improvement in assessment outcome and a lower rebate, while a worsened benefit rating led to increased rebates.

References
G-BA resolutions collected from www.g-ba.de, last accessed October 18, 2018;
Price and rebate information from www.lauer-fischer.de, last accessed July 11, 2018