Orphan drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implications

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Objectives

The AMNOG, the legislative framework governing the market access of innovative prescription drugs in Germany, has implicated a paradigm shift in the examination of the value of a pharmaceutical and in the setting of an appropriate reimbursement level for the product. Based on the evidence of available study data, the additional benefit over the existing standard of care is assessed by the most powerful German health authority, the G-BA. Depending on the classification of the benefit category, the pharmaceutical manufacturer negotiates the final refunded price with the umbrella organization of the German statutory health insurances. For orphan drugs, the additional benefit is granted by law, yet there are specific challenges that the manufacturer has to meet. Due to the rareness of the disease, subpopulations are small and study data are scarce. This leads to a considerable uncertainty about the perceived value of the drug and, thus, to intense and sometimes tough negotiations with high rebates in the end. Aim of this study was to investigate how orphan drugs were assessed in the course of the early benefit assessment in Germany in order to identify all relevant obstacles and enable manufacturers to better adapt to these challenges.

Methods

- G-BA resolutions and reasonings of orphan drug assessments up until October 2018 were included in the analysis.
- Based on the published documents, active substances, therapeutic areas, indications and the extent of the additional benefit category were extracted.
- In addition, prices and negotiated rebates were retrieved from the price listing for pharmaceuticals (Lauer-Taxe) in Germany.
- For the comparison of the additional benefit and the negotiated rebate, the highest benefit category per assessed active substance was used.

Results

Figure 1: Status of early benefit assessments with orphan drugs

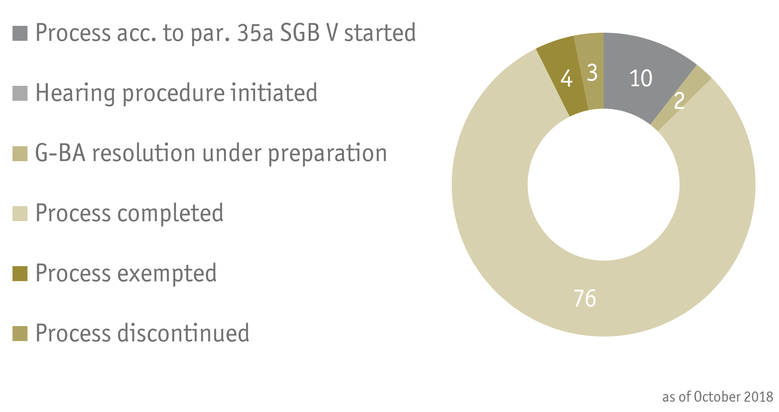


Figure 2: Completed AMNOG procedures of orphan drugs per year from 2011 until October 2018

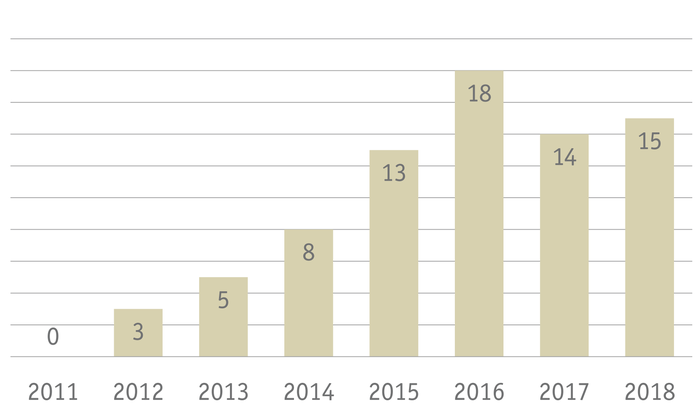
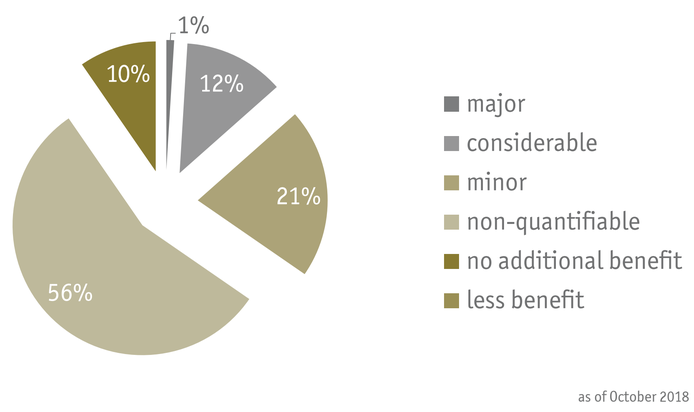


Figure 3: Additional benefit categories granted by G-BA for orphan drugs' subpopulations



Since the introduction of AMNOG and until October 2018, 76 orphan drug procedures have been completed by the G-BA, for 2 the G-BA resolution is under preparation and 10 have recently started (see Figure 1).

As Figure 4 demonstrates, the main therapeutic area was oncology covering more than half of the active substances, followed by inherited metabolic disorders. All further disease areas were not particularly strongly represented.

As there have been reassessments due to indication extensions and exceedances of the 50 million Euro threshold in sales, a total of 66 different active substances have been assessed. With a few exceptions, most reassessments took place in the field of oncology and metabolic disorders, for example brentuximab vedotin, pasireotid and ivacaftor due to label extensions and pomalidomid, ibrutinib, daratumumab, carfilzomib, ruxolitinib and macitentan due to sales exceeding 50 million Euro.

Several early access instruments to expedite development and regulatory review have been in place for many years and, as demonstrated in Figure 2, the market authorizations of orphan drugs and market entries in Germany are continuously increasing. But these centralized European programs often lead to data which do not meet the evidence requirements for pricing and reimbursement (P&R) decisions at the national level.

The difference between the EMA and HTA standards becomes particularly clear when looking at the results of the benefit assessment. While the EMA accepts clinical data out of studies which do not score the highest evidence class (phase II, single-armed, no active comparator), and which use promising albeit not validated surrogate endpoints, IQWiG and G-BA in principle demand the highest possible evidence level. Thus, it becomes clear that in the majority of cases, the G-BA decided to award the non-quantifiable contemporary for the product under consideration. In 22 (21%) so far assessed subpopulations, the additional benefit was minor, in 58 (56%) non-quantifiable, in 13 (12%) considerable and in only 1 (1%) major. In addition, the G-BA granted no additional benefit for 10 (10%) assessed subpopulations after the sales of the corresponding active substances exceeded the 50 million Euro and thus had to be reassessed in comparison to an appropriate comparative therapy (see Figure 3).

By October 2018, 58 of currently 76 early benefit assessment procedures fully paced the AMNOG legislation comprising the assessment of additional benefit extent as well as associated price negotiations. The negotiated (or arbitrated) price becomes effective in retrospect starting with the 1st day of the 13th month after market launch, while manufacturers are free to set the price for the first 12 months. So far, the prices of 6 orphan drugs have been arbitrated. These were pomalidomide, siltuximab, ataluren, idebenon, blinatumomab and tasimelteon.

Rebates range from 14.35% up to 89.50%. As Figure 5 shows, there is no obvious link between the benefit category and the negotiated rebate. The arbitrated rebates, on the other hand, are among the higher ones. Rebates for oncological products are widely distributed. The highest one of 89.50% was negotiated in the case of venetoclax for the two smallest of a total of seven package sizes. The largest, on the other hand, only received a very small rebate of 21.26%. Nusinersen is the only active substance with a major additional benefit that has so far been granted by the G-BA which was rewarded with a small rebate of only 15.79%.

Figure 4: Therapeutic areas of orphan drugs' benefit assessments since 2011 until October 2018

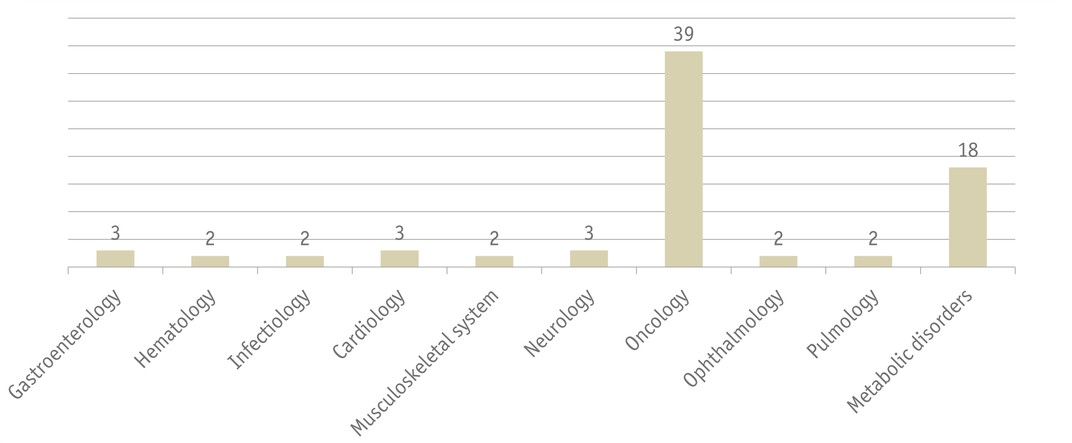
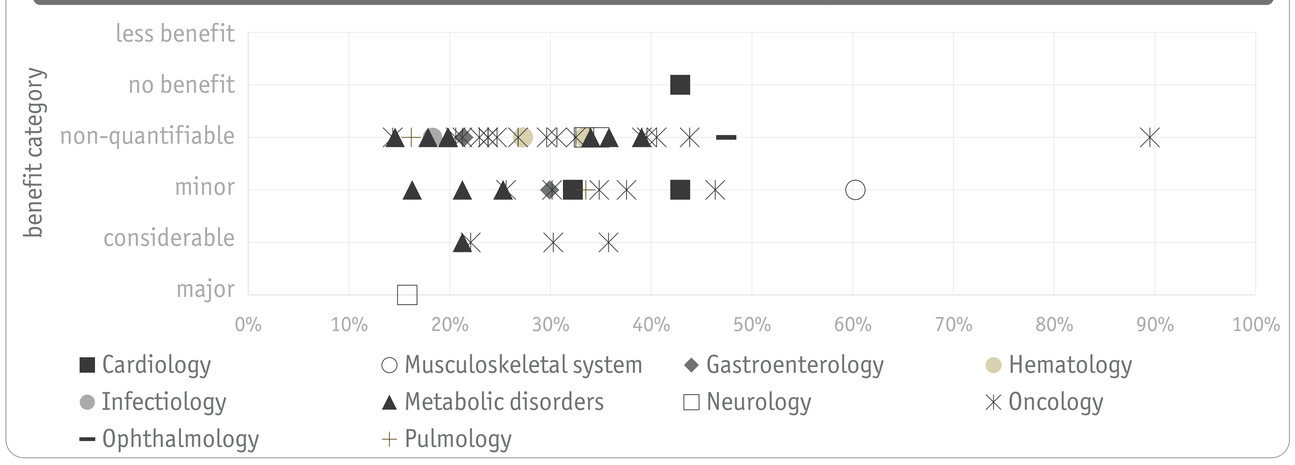


Figure 5: Negotiated rebates for orphan drugs per highest benefit category



Conclusion

- The legal link of the orphan drug designation to the market authorization with the implications of a faster access (conditional marketing authorization) for patients certainly leads to the fact that **54% of the assessments result in a non-quantifiable benefit** which usually also means that pending further scientific data, a classification in one of the other categories is not possible. Since the value of the product is often ambiguous due to the non-quantifiable additional benefit category, the written statement and the oral hearing as well as the involvement of stakeholders – including patient representatives within the G-BA – is of highest importance in the process. This makes the early integration of KOLs , patient representatives and other advocacy groups all the more important.
- In some cases, the G-BA puts a time limit on its resolution to be able to conduct a further assessment after a period of post-marketing experience. In some of these cases (e.g. asfotase alfa, sebelipase alfa and idebenon), the G-BA requested the setup of a **German registry** in addition to the EMA registry to be able to collect data of German patients. Based on these data the new benefit assessment will be conducted after the current resolutions have expired.
- Besides **the procedure-specific challenges** by the formal requirements, the budget impact, comparable drugs, the level of European prices and the heterogeneity of evidence in possible subpopulations, the pharmaceutical manufacturers have to consider **the technical issues** like the package size, the notification requirements by the IFA and provision and service levels.
- For orphan drugs , it can be expected, that the situation will get tougher in the future. All kinds of different stakeholders, not only the payers but also the physicians claim that a further **'orphanization'** should be counteracted by even tougher regulations. This would include a full benefit assessment, requiring a full dossier and a high evidence leveled study with validated endpoints and data against the standard of care in the field of application.
- In the future, it becomes even more important than before, to design and execute a **stringent and smart strategy** and to involve the market access perspective as early in the process of research and development as possible. Internal processes should be aligned and the collaboration between R&D, Medical, HEOR, Regulatory, Legal and Pricing & Reimbursement (P&R) departments should be especially fostered to answer the arising challenges.

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1 https://www.g-ba.de/informationen/nutzenbewertung/ | 2 https://www.cgm.com/lauer-fischer/index.de.jsp

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