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Evidence on orphan drugs[1]

Extract

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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IQWiG employees

- Philip Kranz
- Gertrud Egger
- Thomas Kaiser
- Fabian Lotz
- Can Ünal
- Siw Waffenschmidt

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Executive summary

The topic of evidence on orphan drugs was investigated within the scope of the general commission.

Background

Orphan drugs have a special position in the German Act on the Reform of the Market for Medicinal Products (AMNOG[2]). Orphan drugs do not undergo the regular benefit assessment procedure after market access, since, according to § 35a of the German Social Code Book (SGB[3]) V (1) Sentence 11, their added benefit is already considered proven with the approval at the European level. The Federal Joint Committee (G-BA[4]) assesses the evidence submitted by the pharmaceutical company; no standard care (called "appropriate comparator therapy") is specified for these procedures (in the following, they are referred to as "limited assessments"). If, on the basis of this evidence, no quantification by the G-BA of the added benefit of the orphan drug into the categories "minor", "considerable" or "major" is possible, the drug is granted a "non-quantifiable" added benefit. A regular benefit assessment of an orphan drug versus the appropriate comparator therapy is only conducted if an annual revenue threshold of 50 million euro is exceeded, if the pharmaceutical company relinquishes the orphan drug status or if the disease no longer meets the prevalence criteria of a rare disease. In the regular benefit assessment, "no added benefit" or even "lesser benefit" of an orphan drug versus the appropriate comparator therapy can also be determined.

Research question

The aims of the present investigation are

- the systematic comparison of the (fictitious) added benefit in limited assessments and the inferred added benefit of an orphan drug versus the appropriate comparator therapy in regular benefit assessments of orphan drugs, and
- the description of the available evidence in regular benefit assessments versus previous limited assessments

Methods

Information retrieval

For the present project, all assessments of an orphan drug were used for which a regular benefit assessment according to § 35a SGB V was available. This could include, on the one hand, the first regular benefit assessment of the respective orphan drug after market access and, on the other, any subsequent assessments in the case of one or more extensions of the therapeutic indication, provided that the orphan drug status still existed at the European level at the time of

[2] Arzneimittelmarktneuordnungsgesetz

[3] Sozialgesetzbuch

[4] Gemeinsamer Bundesausschuss

this extension. The respective decisions of the G-BA were decisive for the determination of the assessment result.

To ensure a systematic presentation, we used the database of the G-BA on benefit assessments according to § 35a SGB V with the integrated filter on orphan drugs. All decisions on orphan drugs with their associated procedures were considered according to the above criteria.

Information synthesis

For the primary analysis, assessments were used where both a result according to § 35a SGB V (1), Sentence 11 (limited assessment) and that of a regular benefit assessment were available. The added benefit inferred in each case in a limited assessment was compared with that inferred in the subsequent regular benefit assessment. In addition, the underlying evidence base was described for these assessments.

For the secondary analysis, those assessments were considered where only a regular benefit assessment was available and it was examined how often no added benefit was determined for the orphan drug. This resulted in the proportion of potentially discrepant assessments to fictitious limited assessments that were not conducted because the revenue threshold had previously been exceeded. For these assessments, the underlying evidence base in each case was also described.

The assessment results on the added benefit were considered according to the distinction in the respective G-BA decision (i.e. within a decision, if necessary, at the level of several research questions).

Results

Information retrieval results

Information retrieval identified N = 20 orphan drugs for which at least one regular benefit assessment had been conducted. These orphan drugs were assessed in a total of n = 79 research questions. For 41 questions, both a limited assessment and a regular benefit assessment had been conducted (relevant for the primary analysis). One question was excluded from the primary analysis because it was the subject of the limited assessment, but not of the subsequent regular benefit assessment. For 37 questions, only a regular benefit assessment was available (relevant for the secondary analysis).

Results of the primary analysis

The primary analysis considered assessments where both the result of a limited assessment and that of a regular benefit assessment were available (41 research questions).

Results of the limited assessments and the regular benefit assessments

In the limited assessments of the 41 research questions on orphan drugs, an added benefit with the extent “non-quantifiable” was most commonly inferred (51%; n = 21). The extent of added benefit was minor in 32% (n = 13) of the questions, considerable in 15% (n = 6), and major in

2% (n = 1). In contrast, in the regular benefit assessments of these research questions on orphan drugs, no added benefit ("not proven") was most commonly inferred (54%; n = 22). The extent of added benefit was non-quantifiable in 15% (n = 6) of the questions, minor in 7% (n = 3), considerable in 22% (n = 9), and major in 2% (n = 1).

Agreement between the results of the limited assessments and regular benefit assessments

Overall, 27% (n = 11) of all research questions relevant for the primary analysis showed an identical extent of added benefit between the limited and the regular benefit assessments. In 73% (n = 30) of cases, the extent of added benefit deviated between the two types of assessments. Among these, a greater extent of added benefit for the orphan drug was inferred in 14% (n = 6) of the research questions in the regular benefit assessment; in 5% (n = 2) the extent of added benefit was lower, and in 54% (n = 22) no added benefit was shown for the orphan drug.

Separated by drugs, an added benefit was inferred for only 25% of the 20 orphan drugs (N = 5; ivacaftor, ruxolitinib, nintedanib, olaparib, and carfilzomib) in all research questions of the regular benefit assessment. In most cases, however, the extent of added benefit deviated between the two types of assessments. For the remaining 75% (N = 15) of orphan drugs, in each case no added benefit was shown in the regular benefit assessment for at least 1 research question. For 45% (N = 9) of the orphan drugs, an added benefit was not determined in any research question.

Evidence base of the results of the limited assessments and regular benefit assessments

For the limited assessments, randomized controlled trials (RCTs) were available as an evidence base for 68% (n = 28) of the research questions. Non-randomized studies (non-RCTs) were available for 27% (n = 11) of the questions, and no (usable) data were submitted for 5% (n = 2) of the questions. Adjusted indirect comparisons or evidence transfers were not available in any assessment. The quantification of the added benefit by the G-BA into the categories "minor", "considerable" or "major" was exclusively based on RCTs. In the case of non-RCTs or no (usable) data, a non-quantifiable added benefit was always inferred.

The evidence base of the regular benefit assessments of orphan drugs showed that for 39% (n = 16) of the research questions, direct comparative evidence from RCTs was available on orphan drugs versus the appropriate comparator therapy. For 5% (n = 2) of the questions, an adjusted indirect comparison was used. For 2% (n = 1) of the questions, usable data from non-RCTs were available. An evidence transfer was performed for 5% (n = 2) of the questions. No (usable) data were available for 49% (n = 20) of the questions. In the regular benefit assessment, the quantification of the added benefit into the categories "minor", "considerable" or "major" was also exclusively based on RCTs.

For 66% (n = 27) of the 41 research questions, no new data were available for the regular benefit assessment versus the limited assessment. In these cases, mostly no added benefit was inferred (70% [n = 19] of the 27 questions). Data from newly conducted studies were available for 10%

(n = 4) of the questions. New data from studies already known were available for 17% (n = 7) of the questions. If new studies or new data were available, an added benefit was always inferred in the regular benefit assessment. New usable adjusted indirect comparisons were available for 7% (n = 3) of the questions; an added benefit was not inferred for any of them.

Results of the secondary analysis

For the secondary analysis, assessments of orphan drugs were considered where only a regular benefit assessment was available. This was, for example, the case for a newly approved therapeutic indication of an orphan drug if its revenue had already exceeded the threshold of 50 million euro before approval of the new therapeutic indication.

Results of the regular benefit assessments

In the regular benefit assessments of the 37 research questions, the conclusion "no added benefit" was most commonly inferred (54%; n = 20). The extent of added benefit was non-quantifiable in 22% (n = 8) of the questions, minor in 5% (n = 2), considerable in 11% (n = 4), and major in 8% (n = 3).

The results are consistent with those of the regular benefit assessments from the primary analysis.

Evidence base of the results of the regular benefit assessments

For 32% (n = 12) of the research questions, direct comparative evidence from RCTs was available for the orphan drug versus the appropriate comparator therapy. For 3% (n = 1) of the questions, usable data from an adjusted indirect comparison were available. Evidence transfers were used for 19% (n = 7) of the questions. No (usable) data were available for 46% (n = 17) of the questions. Non-RCTs were not considered. The quantification of added benefit into the categories "minor", "considerable" or "major" was based on RCTs in 89% (n = 8) of the 9 questions.

The results are largely consistent with those of the regular benefit assessments from the primary analysis.

Summary of the primary and secondary analysis

In a further analysis, the results of the primary and secondary analysis on regular benefit assessments were summarized (78 questions in total). This analysis enables a summary of the evidence on orphan drugs versus standard care (= appropriate comparator therapy) in the case of a regular benefit assessment.

Summary of the results of the regular benefit assessments

The frequencies of the extent of added benefit inferred are comparable to those of the primary and secondary analyses. No added benefit ("not proven") was most commonly inferred in the research questions (54%; n = 42). The extent of added benefit was non-quantifiable in 18% of the questions (n = 14), considerable in 17% (n = 13), minor in 6% (n = 5), and major in 5% (n = 4). A "lesser benefit" was not inferred in any question.

At the drug level, an added benefit was only inferred for 15% (N = 3) of the 20 drugs (ruxolitinib, nintedanib and olaparib) in all the research questions assessed during the period under review. For the remaining 85% (N = 17), no added benefit was inferred in at least 1 question. In the limited assessment, at least an added benefit with the extent "non-quantifiable" was granted or would have been granted for all of these questions and thus all 20 drugs.

Summary of the evidence base of the regular benefit assessments

The evidence base shows that for 47% (n = 37) of the 78 research questions, most commonly no usable data were available for the regular benefit assessment of the orphan drugs considered here. The fact that no usable data were available was also the most common reason for the conclusion "added benefit not proven" (88% [n = 37] of the 42 questions with this assessment).

For 36% (n = 28) of the 78 research questions, data from RCTs were available for the assessment. The quantification of the added benefit into the categories "minor", "considerable" or "major" was almost exclusively based on RCTs, with the exception of 1 question.

Conclusion

The present report shows that specifying a fictitious added benefit at market access of orphan drugs is misleading in more than half of the cases, as no proof of added benefit is shown in subsequent regular benefit assessments. This not only leads to misleading communication about the added benefit of new orphan drugs, but also discriminates against existing treatment options for rare diseases by letting them appear to be inferior through the fictitious added benefit granted to orphan drugs. Furthermore, this general fictitious added benefit prevents a distinction between orphan drugs with and without real progress for patient care. The misleading communication on added benefit is maintained for years and in some cases not corrected if the revenue threshold of 50 million euro per year is not exceeded or the pharmaceutical company voluntarily relinquishes the orphan drug status. Overall, a main goal of AMNOG, namely, "separating the wheat from the chaff", is prevented for orphan drugs through the privilege of a fictitious added benefit.

The evidence base shows that RCTs are also possible for orphan drugs. However, many of these RCTs have so far not focused on questions relevant to health care (comparison of orphan drugs with existing treatment options in respect of patient-relevant outcomes), but in particular address the criteria for approval. Efforts must therefore be undertaken to ensure that in future, patient-relevant and health care-related questions are increasingly considered in the planning and conduct of studies. In particular, routine data collection according to the German Law for More Safety in the Supply of Medicines (GSAV[5]) should be expanded to include the possibility of conducting pragmatic (registry-based) RCTs. This could also promote the development of the registry landscape in Germany, with the aim of clarifying open health care questions as promptly and reliably as possible in the future.

[5] Gesetz für mehr Sicherheit in der Arzneimittelversorgung

The full working paper (German version) is published under https://www.iqwig.de/projekte/ga21-01.html.