Factors impacting GKV rebates for Orphan Drugs (OD) in Germany – a decision analysis using the CRA RADAR database

Andras Ruppert
Charles River Associates, Munich, Germany – aruppert@crai.com

CRA Charles River Associates

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Introduction and Objective

The European Orphan Medicinal Products Regulation, issued in 2000, encouraged the development of treatments for rare diseases. Twenty-five years later, over 200 drugs with orphan designation (ODs) have been approved by the European Medicines Authority (EMA).

The benefit assessment by the German Gemeinsame Bundesausschuss (G-BA) acknowledges the benefit of ODs by granting a non-quantitative added benefit by default. Only when annual sales volumes exceed €30 million is a new AMNOG assessment performed on the same scientific grounds as for non-ODs. Rebate negotiations on the manufacturer (MNF)-set list price between manufacturers and the German statutory health insurance (GKV) have no exceptions for ODs. However, the default 'non-quantifiable added benefit' rating ensures a slightly different starting point for drugs not exceeding the budgetary threshold for ODs.

After 14 years of AMNOG process, sufficient data should be available to analyze its impact on reimbursement prices via GKV rebates for drugs with orphan designation, as well as to identify which quantifiable factors have had the biggest impact on GKV rebates for ODs.

Methodology

The analysis was performed using data from the RAre Disease Assessment Review database (RADAR), a proprietary CRA database, encapsulating data from, e.g., US, Canada, and top 5 European countries. It includes 164 ODs that received EMA Marketing Authorization (MA) between July 1, 2013, and September 30, 2024. For Germany, the database collects:

- Publicly available information on EMA MA
- OD's first indication and prevalence rates used by EMA and G-BA assessments
- HTA outcomes (G-BA ratings)
- Manufacturer-set list and reimbursed net unit prices as published in Lauer Taxe
- Calculated annual treatment cost based on SmPC dosing and Lauer Taxe unit price
- Negotiated GKV rebates for all ODs that received EMA MA

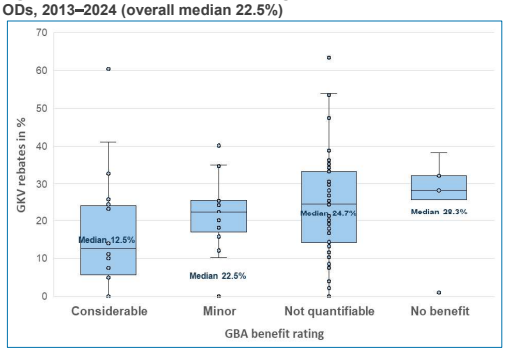
49 ODs were excluded from the German analysis due to missing G-BA assessments, missing published list prices, and/or missing GKV rebates /negotiated reimbursed prices in Lauer Taxe, leaving 115 ODs for the analysis.

The analysis looked at G-BA ratings, clinical comparator, prevalence, MNF-set list prices, different groups of indications (oncology vs non-oncology), and their relation to rebates achieved in negotiations between manufacturers and GKV.

Results

Negotiated GKV rebates for ODs seem to be impacted by G-BA benefit ratings, not the clinical trial comparator per se

Fig. 1: Correlation of G-BA benefit ratings and GKV rebates for 115 ODs, 2013–2024 (overall median 22.5%)



Although the low absolute numbers, particularly in the 'no benefit' group, have their limitations, the median analysis indicates that GKV negotiators adhere to their mandate. The G-BA benefit ratings appear to be reflected in the negotiated rebates, especially for the highest (12.5% median rebate) and the lowest rating (28.3% median rebate), and an overall median rebate of 22.5%.

Overall, the message of 'the better the rating, the lower the rebate,' seems to apply to ODs, as it aligns with the objectives of the AMNOG process.

The same is not true for presented clinical evidence and GKV rebates, where natural history as comparator results in the lowest (mean 20%), single arm trial in the highest GKV rebates (mean 24%) . Table 1 tries to link clinical comparators and G-BA rating. Only clear message is that single arm trials do not allow for a minor or considerable benefit rating.

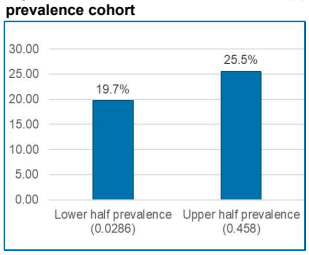
Tab. 1: Clinical comparators and G-BA ratings for 115 ODs

Benefit vs. comparator	NH	BSC	SOC	PBO	SAT
Considerable benefit (n=18)	2	1	7	8	
Minor benefit (n=15)			5	10	
Not-quantifiable benefit (n=77)	6	1	24	25	21
No benefit (n=5)		1	1	1	2

NH: natural history; BSC: best supportive care; SOC: standard of care; PBO: placebo; SAT: single-arm trial.

Negotiated GKV rebates for ODs are impacted by disease prevalence

Fig. 2: Mean GKV-rebate for lower and upper prevalence cohort



All 115 ODs were divided into above and below median prevalence (0.074 p. 10,000), with mean prevalence of 0.0286 in the lower and mean prevalence of 0.458 in the upper half of prevalence groups (p<.001).

The mean GKV rebate in the lower prevalence group is 19.7% (SD 13.1). The GKV rebate in the higher prevalence group is 25.5% (SD 12.9). The difference is statistically significant (p<.02).

Negotiated rebates seem to be impacted by manufacturer-set list price pre-negotiation

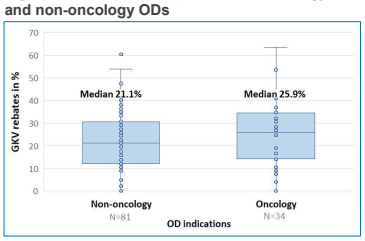
Tab. 2: GKV rebates across different ranges of annual cost in the sample of 115 ODs

OD clusters based on annual treatment cost (atc) calculated from MNF-set list prices and SmPC dosing regimen	GKV rebate median (IQR)
atc >€500,000 (n=19; median atc €731,194)	27.2% (19.3)
atc €100,000-€500,000 (n=48; median atc €255,980)	24.6% (22.5)
atc <€100,000 annual cost (n=48; median €59,850)	21.4% (17)

The analyses indicates some level of price sensitivity, with higher median rebates for higher atc / MNF-set price levels. However, one might have anticipated a greater rebate disparity (and statistical significance) between the lower and upper third, considering the more than fivefold difference in annual treatment costs.

Negotiated GKV rebates seem to be impacted by different OD indications (oncology vs. non-oncology)

Fig. 3: GKV rebates comparison for oncology and non-oncology ODs



All 115 ODs were divided into an oncology (34 ODs) and a non-oncology (81 ODs) group.

The analysis seems to indicate that manufacturers of oncology ODs must accept higher GKV rebates (median 25.9%) compared to manufacturers of non-oncology ODs (median 21.1%).

Tab. 3: G-BA ratings and mean GKV rebates for oncology vs. non-oncology ODs

G-BA rating (n)	Oncology ODs (34)	Non-onc. ODs (81)
Considerable added benefit (18)	18.3% (8)	15.4% (10)
Minor added benefit (15)	25.7% (3)	20.4% (12)
Non-quantifiable benefit (77)	25.9% (22)	22.5% (55)
No benefit (5)	32.1% (1)	30.8% (4)

Tables 3 and 4 indicate that oncology ODs faced higher rebates compared to non-oncology ODs despite equal, potentially slightly better GBA-ratings, and despite lower mean MNF-set list prices (expressed through mean annual treatment cost).

Tab. 4: Comparison of annual costs and GKV rebates for oncology vs. non-oncology ODs

	Oncology ODs (34)	Non-onc. ODs (81)
Mean annual cost at mnf-set list prices	€236,146	€355,054
Mean GKV rebate	24.6%	21.6%

While prevalence impact rebates overall, indication analysis showed lower mean prevalence of oncology ODs (0.1561) compared to non-oncology ODs (0.2419). Still, rebates are higher for oncology OD.

Conclusions

Tab. 5: Ranking of key impact factors by % difference to mean GKV rebate (22.5%) across 115 ODs

In the table, the mean=median rebate of 22.5% across all 115 ODs was set as the benchmark. The identified mean GKV rebate linked to each impact factor is presented as a percentage deviation from that overall mean benchmark. Only factors with more than 10% deviation from mean are shown in the table.

G-BA rating: 'considerable added benefit'	-44%
G-BA rating: 'no added benefit'	+25%
Manufacturer set list price >€500,000 annual cost	+20%
Oncology indication	+15%
Prevalence above median*	+13%
Prevalence below median*	-12%
Clinical comparator: 'Natural History'	-10%
G-BA rating: 'not quantifiable added benefit'	+10%

**Statistically significant difference*

Strong G-BA benefit ratings seem to have the largest impact on achievable GKV rebates – in both directions. Negotiators, also for ODs, seem to use the added benefit identified by G-BA as basis for negotiations, following the objective set out for the AMNOG process.

Another objective of the AMNOG process, the reduction of high list prices, also appears to be achieved, as drugs with the highest MNF-set list prices seem to face the highest rebates. However, the size of the difference in rebates relative to the differences in annual costs indicates low price sensitivity for ODs. Higher list prices seem to result in higher net prices.

Despite already low patient numbers, prevalence seems to be a key driver of rebates, suggesting that budget impact (MNF-set price x patient numbers) is also relevant for OD negotiations.

Negotiations for ODs with oncology indications seem to result in higher rebates compared to non-oncology, despite better ratings, lower prevalence, lower mean MNF-set list prices. A potential reason might be the availability of indirect price comparators in adjacent non-orphan indications.

Other, non identifiable factors might impact GKV rebates, such as perceived unmet need, as potentially indicated by the lower rebates achieved by those non-oncology ODs for which natural history (NH) is accepted as clinical evidence. Further research is needed, especially into non-quantifiable aspects that impact rebate negotiations.

References

Factors impacting GKV rebates for Orphan Drugs in Germany – Part 1 of a deep dive decision analysis using the CRA RADAR database; A. Ruppert; Charles River Associates; www.crai.com.

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