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The impact of non-comparative data for non-orphan drugs on HTA and pricing outcomes in Germany: can an added benefit ever be proven?

K. CULLEN, PhD[1], I. OWENS-SMITH[1].
[1]RED NUCLEUS, London, UK

INTRODUCTION

Germany has traditionally been viewed as a priority market for launch of novel medicinal products due to pre-AMNOG free pricing, and downstream positive implications for global list price potential through International Reference Pricing (IRP).

However, the 2023 Cost-Containment Bill (GKV-Finanzstabilisierungsgesetz) means Health Technology Assessment (HTA) outcomes are now more explicitly linked to price achievability in Germany. Without appropriate direct comparator data from pivotal studies, most products will receive a "no added benefit" rating, limiting list price potential to the most economical comparator minus 10%. This has led to increasing downward pressure for novel therapeutics in Germany, with knock-on global effects.

The Federal Joint Committee (G-BA) acknowledges the difficulties in generating comparative data for orphan drugs by awarding a minimum rating of "unquantifiable added benefit". However, there are no allowances for non-orphan drugs in small populations that may experience similar challenges.

OBJECTIVES

The aim of this analysis was to understand the impact of non-comparative data on G-BA HTAs of non-orphan drugs for small populations and the subsequent price impact following post-AMNOG negotiations.

METHODS

Published benefit assessments were extracted from the G-BA website. Selection criteria consisted of first indication, non-orphan drugs with a population size of <25,000, without direct comparative data (or where direct comparative data was deemed inappropriate by the G-BA), that underwent HTA from 2021, and with completed post-AMNOG pricing negotiations.

RESULTS

Using the aforementioned selection criteria, HTAs for twelve drugs were identified **(Table 1)**. Appropriate comparator therapy (ACT) was defined as specific comparator therapies in nine of these assessments, whilst physician's choice, best supportive care (BSC), and watch and wait were each specified once **(Table 2)**.

Looking at the types of data submitted by manufacturers, two did not include any form of comparative data, meaning clinical effectiveness could not be compared to ACT, resulting in a "no added benefit" rating **(Table 2)**.

Indirect comparative data was submitted to the G-BA for 7/12 drugs, but inappropriate use of comparators or methodology resulted in rejection of >50% of these analyses. For the three drugs with accepted indirect comparative data, clinical effectiveness was not deemed sufficiently differentiated to demonstrate an added benefit **(Table 2)**.

Although three drugs were studied in randomised clinical trials (RCTs), inappropriate use of comparators meant they were unable to demonstrate appropriate comparative clinical effectiveness and, again, received a "no added benefit" rating **(Table 2)**.

Finally, following pre-AMNOG free-pricing and subsequent post-AMNOG pricing negotiations, the list price of the identified drugs decreased by an average of 40% for products remaining on the German market.

Drug	Therapeutic Area	Eligible Population	1st Price Date
Entrectinib	Solid tumours, NTRK gene fusion	390 – 770	May 2021
Berotralstat	Hereditary angioedema	140 – 430	Jun 2021
Dostarlimab	Endometrial carcinoma	230 – 3360	Jun 2021
Pralsetinib	Non-small cell lung cancer	170 – 510	Dec 2021
Zanubrutinib	Waldenström's disease	450 – 1050	Dec 2021
Lusutrombopag	Thrombocytopenia	1790 – 24130	Dec 2021
Amivantamab	Non-small cell lung cancer	9 - 26 in 2022	Jan 2022
Duvelisib	Follicular lymphoma & chronic lymphocytic leukaemia	1010 – 14500	Feb 2022
Sotorasib	Non-small cell lung cancer	591 – 1157	Feb 2022
Tepotinib	Non-small cell lung cancer	540 – 910	Mar 2022
Anifrolumab	Systemic lupus erythematosus	4600 – 18500	Apr 2022
Inebilizumab	Neuromyelitis optica spectrum disorder	460 – 980	Aug 2022

Table 1. *Overview of the medicinal products included in the present analysis. HTA assessments were extracted from the G-BA website, including products launching in a first indication, without orphan drug designation, with a population of <25,000, without comparative data that underwent G-BA assessment from 2021, and with completed post-AMNOG pricing negotiations.*

Drug	G-BA Defined Comparator (ACT)	Comparative Data	Added Benefit
Entrectinib	Crizotinib	MAIC accepted; outcome not significant	None
Berotralstat	C1 esterase inhibitor	None	None
Dostarlimab	Best supportive care	MAIC without a bridge comparator; ITC vs. individual patients and registry data	None
Pralsetinib	Pembrolizumab; nivolumab; chemotherapy	MAIC accepted; outcome not significant	None
Zanubrutinib	Ibrutinib; chemotherapy/steroid	RCT vs. inappropriate comparator	None
Lusutrombopag	Watch and wait	Meta-analysis (accepted) of double-blind RCTs but outcome not significant	None
Amivantamab	Docetaxel ± nintendanib	Non-adjusted/non-randomized ITC based on registry	None
Duvelisib	Patient-individual therapy	None	None
	Ibrutinib; venetoclax + rituximab; chemoimmunotherapy; patient-individual therapy	RCT vs. inappropriate comparator	None
Sotorasib	Docetaxel; pemetrexed; nivolumab; pembrolizumab; atezolizumab; docetaxel + nintedanib; patient-individual therapy	RCT vs. inappropriate comparator	None
Tepotinib	Cisplatin; carboplatin; monotherapy + gemcitabine or vinorelbine	None	None
Anifrolumab	Belimumab	MAICs based on off-label comparator data with an incomplete study pool and insufficiently similar subpopulations	None
Inebilizumab	Physician's choice	MAIC vs. only one appropriate comparator	None

Table 2. *Manufacturer-submitted data type and HTA outcome. Accepted data in green; unacceptable data in red. ACT: Appropriate Comparator Therapy; BSC: Best Supportive Care; ITC: Indirect Treatment Comparison; MAIC: Matching-Adjusted Indirect Comparison; RCT: Randomised Clinical Trial.*

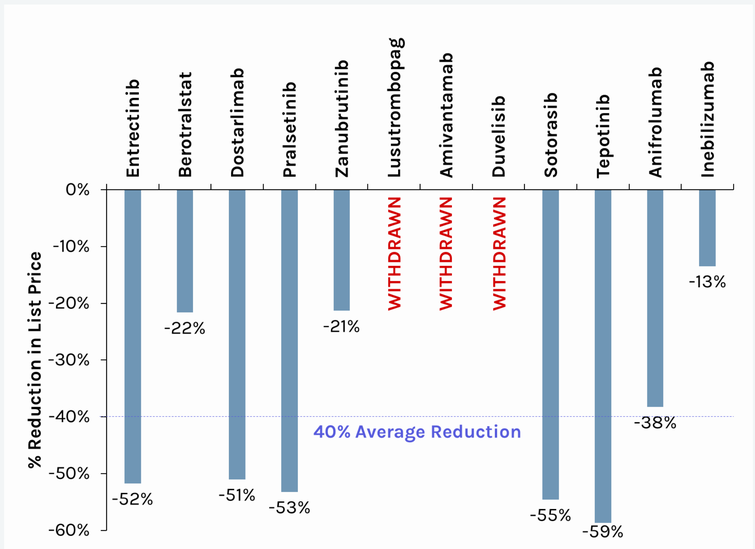

Figure 1. *Annual list price reduction following AMNOG assessment for products without a randomised clinical trial versus appropriate comparator therapy. Calculated using maintenance dosing regimen, assuming 70kg patient weight.*

Importantly, three products withdrew from the market, potentially due to an inability to agree an acceptable price with the GKV-SV statutory health insurers **(Figure 1)**.

CONCLUSIONS

In our analysis, no non-orphan drugs without appropriate direct comparative data obtained a positive added benefit rating, even when indirect comparisons were provided.

Although the G-BA can accept adjusted indirect treatment comparisons and meta-analyses in principle, stringent methodological requirements often result in rejection of comparative analysis and a "no added benefit" HTA rating.

In cases where the G-BA accepts indirect comparative data, difficulties arise in demonstrating sufficiently differentiated treatment effects to overcome systematic bias and successfully demonstrate additional benefit.

SIGNIFICANCE

During product development, manufacturers often focus on the hurdles to achieving regulatory approval, where there is no formal requirement for comparative data. However, this limits a drug's ability to demonstrate comparative clinical effectiveness within European markets such as Germany, with downstream implications on HTA evaluations and pricing negotiations.

Our findings highlight the importance for manufacturers to think beyond regulatory approval and to consider the pricing and access implications of non-comparative data for non-orphan drugs early in the product lifecycle.

REFERENCES

1. HTA assessments accessed through the G-BA website, online at https://www.g-ba.de/
2. Prices sourced from GlobalData, online at https://login.globaldata.com/

Corresponding author contact details: **Isobel Owens-Smith** – Consultant, Market Access & Commercialization Services - iowens@rednucleus.com or www.rednucleus.com/macs