AMNOG Benefit Assessment for Oncologic and Orphan Drugs in Germany: Implications for Price Discounts

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BACKGROUND

- The Act on the Reform of the Market for Medical Products (AMNOG) (*Arzneimittelmarkt-Neuordnungsgesetz*) became effective in 2011, and upon market registration, pharmaceutical companies are obliged by law to submit a benefit dossier to the Federal Joint Committee (FJC) in order to prove the existence of a patient-relevant medical benefit in mortality, morbidity, and health-related quality of life (HRQoL).
- The acceptance of a patient-relevant medical benefit by the FJC is crucial, since only companies with proven and accepted benefit by the FJC are allowed to negotiate a discount on the list price with the National Association of Statutory Health Insurances (SpiBu) (*GKV-Spitzenverband*) in addition to a mandatory discount (§130a SGB V).
- Whereas companies are free to set the price for the first 12 months after launch, negotiated discounts become effective immediately after this period.
- Until now, no systematic analyses have been conducted addressing factors that might influence the magnitude of discounting.
- Oncologic and orphan drugs are usually high-priced and therefore are of most interest in this process.

OBJECTIVES

- The aim of this evaluation was to identify potential factors influencing final negotiated discounts for orphan and oncology drugs.

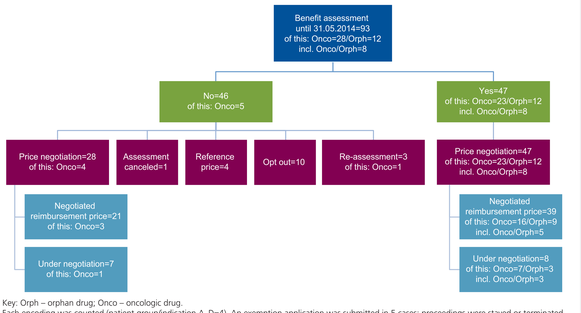
METHODS

- A database containing detailed information on existing discounts or specific indications and data of all dossiers with published benefit ratings until June 2014 was analyzed.
- The official database (Lauertaxe) was used to calculate discounts on ex-factory prices.
- As no official information on discounts is publicly available, the change of ex-factory price before and after the end of negotiations equals the discount.
- All assessments were analyzed with respect to:
  (1) Result of the benefit assessment (major, considerable, minor, non-quantifiable, or no additional benefit)
  (2) Decrease in ex-factory price (prior/after negotiation)
  (3) Existence of HRQoL evidence
  (4) Size of target population (TP)
  (5) Acceptance of appropriate comparator by the manufacturer as set by the FJC
- Descriptive statistics were employed.

RESULTS

- Since AMNOG became effective, 93 benefit assessment dossiers were compiled and a benefit rating was published by the FJC (Figure 1).

Figure 1. Benefit Dossiers With FJC Decision (until 31.05.2014)



Key: Orph – orphan drug; Onco – oncologic drug.
Each encoding was counted (patient group/indication A–D=4). An exemption application was submitted in 5 cases; proceedings were stayed or terminated in 6 cases.

- Until June 2014, 20 price negotiations were completed for oncologic and/or orphan drugs. Of these, 16 were oncologic drugs, including 5 with orphan drug status, and the remaining 4 were orphan drugs but were not oncologic drugs (**Table 1**).
- An additional benefit was granted by the FJC in 21 of 24 cases (some products had more than 1 indication).

Table 1. Overview of Substances With Benefit Assessment and Completed Price Negotiation

ID	Substance	Indication Class	Price Date*	Additional Benefit Y[†]/N (highest/lowest)
1	Bosutinib	Oncologic disease/orphan	01-Apr-14	Yes (not quantifiable)
2	Brentuximab vedotin (A/B)	Oncologic disease/orphan	01-Dec-13	Yes (not quantifiable)
3	Decitabin	Oncologic disease/orphan	01-Nov-13	Yes (minor)
4	Ivacaftor	Metabolic disease/orphan	15-Aug-13	Yes (considerable/minor)
5	Pasireotid	Metabolic disease/orphan	15-Jun-13	Yes (minor)
6	Pirfenidon	Respiratory disease/orphan	01-Jul-13	Yes (not quantifiable)
7	Ruxolitinib	Oncologic disease/orphan	15-Sep-13	Yes (minor)
8	Tafamidis meglumin	Respiratory disease/orphan	01-Feb-13	Yes (minor)
9	Abirateronacetat (incl. LE)	Oncologic disease	01-Feb-13	Yes (considerable/no benefit)
10	Aflibercept	Oncologic disease	01-Mar-14	Yes (minor)
11	Axitinib	Oncologic disease	01-Oct-13	No
12	Cabazitaxel	Oncologic disease	01-Feb-13	Yes (considerable/minor)
13	Critozinib	Oncologic disease	15-Jan-13	Yes (considerable/no benefit)
14	Eribulin	Oncologic disease	01-May-13	Yes (minor)
15	Ipilimumab	Oncologic disease	15-Feb-13	Yes (considerable)
16	Pertuzumab	Oncologic disease	01-Apr-14	Yes (considerable/no benefit)
17	Pixantron	Oncologic disease	01-Jan-14	No
18	Tegafur/glimeracil/oteracil	Oncologic disease	01-Aug-13	No
19	Vandetanib (incl. RA)	Oncologic disease	01-Apr-14	Yes (minor)
20	Vemurafenib (incl. RA)	Oncologic disease	01-Jul-13	Yes (considerable)

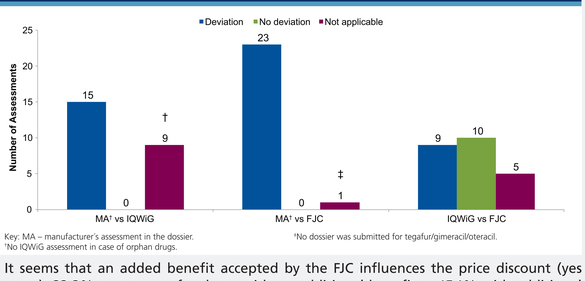
Key: LE – label extension; RA – re-assessment.
A/B – encoding of the dossier patient groups/indications.

*Price data published via Lauertaxe.
[†]For orphan drugs, the additional benefit is predefined by Social Law Book V.

(1) RATING OF THE BENEFIT ASSESSMENT (MAJOR, CONSIDERABLE, MINOR, NON-QUANTIFIABLE, NO ADDITIONAL BENEFIT)

- Rating of additional benefit by the FJC (appraisal) is based on an overall assessment of evidence presented in the dossier for effects on mortality, morbidity, and HRQoL. In addition to self-rating by the manufacturer when the dossier is submitted, an assessment from the Institute for Quality and Efficiency in Healthcare (IQWiG) (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*) and/or the FJC is relevant for the final benefit rating.
- In all cases so far, the rating of the additional benefit by IQWiG and/or the FJC was different from the manufacturer´s assessment (**Figure 2**).

Figure 2. Deviation of Assessment Results (N=24)

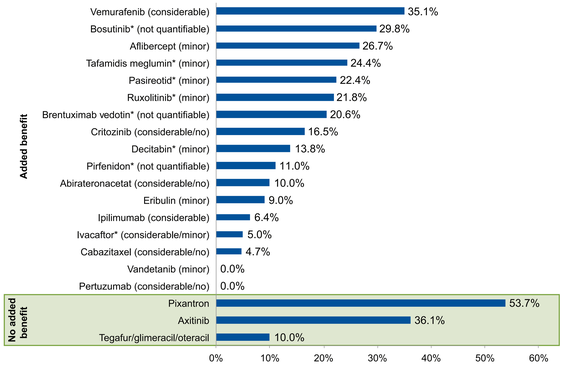


Key: MA – manufacturer´s assessment in the dossier.
[†]No IQWiG assessment in case of orphan drugs.

[‡]No dossier was submitted for tegafur/gimeracil/oteracil.

- It seems that an added benefit accepted by the FJC influences the price discount (yes vs no): 33.3% on average for drugs with no additional benefit vs 15.1% with additional benefit (**Figure 3**).
- Nevertheless, based on current evidence, it is not possible to assess whether a clear equation exists between rating of added benefit and discount level.
- For instance, vemurafenib and pertuzumab both received a benefit rating of "considerable," yet discounts differed tremendously: whereas the discount for pertuzumab was 0%, the manufacturer of vemurafenib had to grant a 35% discount (**Figure 3**).

Figure 3. Published Price Discount (%) per Substance and Status of Added Benefit (by FJC Appraisal)



*Orphan drug
Note: Calculation of price discount: Lauertaxe-published discount in € in relation to manufacturer's ex-factory price in €.

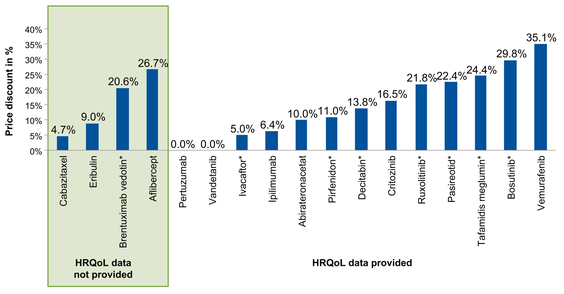
(2) DECREASE IN EX-FACTORY PRICE (PRIOR/AFTER NEGOTIATION)

- In addition to the negotiated discount as a result of official negotiations, a manufacturer might lower the initial price that was set at market launch at their discretion any time before or after finalization of negotiations.
- The published ex-factory price for a drug was lowered after negotiation for pirfenidon (-11%), bosutinib (-30%), tegafur/glimeracil/oteracil (-10%), and vandetanib (-23%).
- After price negotiation, a manufacturer may decide to take their drug out of the market (opt out), as was done for bosutinib.

(3) EXISTENCE OF QUALITY OF LIFE EVIDENCE

- The presence of HRQoL data seems to influence the negotiated discount positively, independent of the outcome or acceptance as a patient-relevant benefit.
- The average discount for drugs with added benefit is lower for oncologic drugs (14.8%) than for orphan drugs (18.3%).
- The highest discount based on evidence that included HRQoL data was 35.1% for an oncologic drug (vemurafenib) (**Figure 4**).

Figure 4. Influence of HRQoL Results by Substances With Accepted Additional Benefit

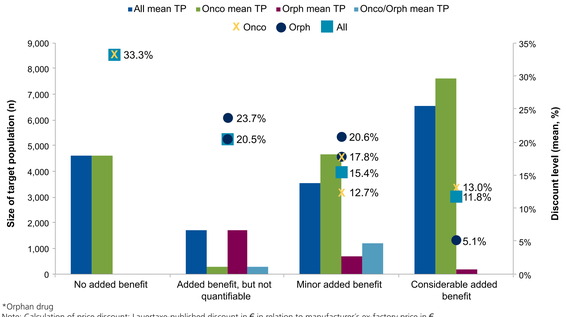


*Orphan drug
Note: Calculation of price discount: Lauertaxe-published discount in € in relation to manufacturer's ex-factory price in €.

(4) NUMBER AND SIZE OF TARGET POPULATION (FIGURE 5)

- In 45.8% (11/24) of assessments, the target population as estimated by the manufacturer was smaller compared to the size calculated by the FJC.
- A "no additional benefit" rating and, perhaps counterintuitively, smaller target populations, tend to be correlated with higher discounts.

Figure 5. Discount Level in Relation to Size of Target Population, Benefit Class, and Drug Status



*Orphan drug
Note: Calculation of price discount: Lauertaxe-published discount in € in relation to manufacturer's ex-factory price in €.

(5) ACCEPTANCE OF APPROPRIATE COMPARATOR AS SET BY THE FJC

- Discounts seem to be smaller if the manufacturer does not deviate from recommendations given by the FJC in advance of the assessment.
- In 3 of 24 evaluated cases, the manufacturer did not follow FJC recommendations regarding the appropriate comparator.
- The mean discount was 12% in the group that followed recommendations compared to 33% in the group that did not follow recommendations.

CONCLUSION AND DISCUSSION

- Based on all evaluated cases, the role of predefined factors regarding final prices and discounts cannot be assessed without leaving questions open.
- Even a small target population (and thus a low budget impact) is not a safe harbor for substantial discounts.
- While the early benefit assessment and appraisal of clinical evidence itself is a very clear and transparent procedure, the process of price negotiations is very unclear.
- Overall, where the Code of Procedure of the FJC defines strict rules for the clinical benefit assessment, no algorithm seems to exist for a prediction of levels of negotiated price discounts.
- Many influencing factors of the negotiations are not directly observable, such as the negotiation skills of the manufacturer, standing of the manufacturer, or good will in situations of high unmet clinical need, to name just a few.
- Early consultation with the FJC and discussion on the appropriateness of the comparator, the patient population, and clinical outcome measures seem to be important and might help to reduce uncertainty.
- In order to support the negotiations, claims data analyses might help to reduce decision uncertainty (eg, on size of target populations) and might influence the assessment of the evidence and price negotiations positively.
- For strategy planning, different strategies need to be prepared while anticipating the perception of the evidence by all the respective parties involved in the negotiation process.
- Health economic modeling (eg, budget impact analysis) might help to fill possible gaps when planning different strategies.