The Quest for the Holy Grail: The potential prediction of GBA decisions on early benefit assessments according to AMNOG - a systematic approach

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Abstract

Objectives: Since 1st January 2011 the German drug market is regulated by the act of the reorganization of the pharmaceutical market (AMNOG). Since then the normal procedure for reimbursement of a new pharmaceutical is an early benefit assessment executed by the Institute for Quality and Efficiency in health care (IQWiG). The joint federal committee (Gemeinsamer Bundesausschuss, GBA) is the reimbursement decision maker whereas the IQWiG has developed methods for the early benefit assessment. Based on the manufacturer submission and on the IQWiG assessment, the GBA determines one of six additional benefit levels to rate the benefit of a new drug versus a predefined comparator.

Methods: To find a systematic approach for the prediction of GBA decisions the algorithms of the 'EValuation of pharmaceutical Innovations with regard to Therapeutic Advantage (EVITA)' approach were applied to recent early benefit assessments. 5 recently published GBA decisions were selected: abiraterone acetate, boceprevir, cabazitaxel, eribulin and telaprevir. An EVITA score was calculated on the basis of the relevant study profiles and outcomes of each selected pharmaceutical, and compared with the published GBA decision.

Results: The assessments for abiraterone acetate (prostate cancer; GBA decision: significant additional benefit; EVITA score: 7.5), boceprevir (hepatitis C; minor to significant additional benefit; 6.5), cabazitaxel (prostate cancer; minor additional benefit, 4.5), eribulin (breast cancer; minor additional benefit, 3), and telaprevir (hepatitis C; minor to significant additional benefit, 10) delivered evidence that there is a correlation between the EVITA score and the GBA decision. An EVITA score between 3 to < 4.5 was connected to a minor additional benefit and a score ≥ 6.5 was connected to a significant additional benefit.

Conclusion: Assessment of the potential therapeutic advantage of a new drug by applying the EVITA algorithms appears to be a feasible approach to predict GBA decisions related to AMNOG early benefit assessments.

Introduction

- On January 1st 2011 the German Law for Reforming the Market for Pharmaceuticals (Arzneimittelmarktneuordungsgesetz - AMNOG) became effective. Due to this law the means of obtaining reimbursement for pharmaceuticals from the German statutory health insurance have changed significantly.
- The prices for pharmaceuticals with new active ingredients will now be fixed during a standard evaluation and potential negotiation process:
  - either through their immediate classification into a reference price group,
  - or through negotiations with the German Federal Associations of Health Insurance Funds ("Spitzenverband der Krankenkassen"),
  - or – in the case that these negotiations fail – through the regulation of a responsible arbitration board.
- The Federal Joint Committee (Gemeinsamer Bundesausschuss, GBA) evaluates the new compound with respect to its additional clinical benefit within three months upon launch of a new pharmaceutical in Germany (launch: time of price submission to Lauer-Taxe). The GBA normally commissions the Institute for Quality and Efficiency in Health Care (IQWiG) with assessing the benefits of the new drug.
- In order to provide evidence for an additional benefit the pharmaceutical companies submit a dossier to the GBA based on the official forms provided by the GBA. The additional clinical benefit needs to be proven versus a specified 'appropriate comparator' defined by the GBA.
- Based on the findings of the IQWiG assessment the GBA determines one of the following six additional benefit levels:
  - (1) major additional benefit
  - (2) significant additional benefit
  - (3) minor additional benefit
  - (4) non-quantifiable additional benefit
  - (5) no additional benefit
  - (6) worse than the comparator
- One of the key questions for pharmaceutical companies is whether it is possible to predict the outcomes of this early benefit assessment through a systematic approach.

Methodology

- Utilizing the algorithm of the 'EValuation of pharmaceutical Innovations with regard to Therapeutic Advantage (EVITA)' [1], developed by the University of Bremen, we investigated whether the level of benefit for selected new pharmaceuticals assessed by the GBA could be predicted systematically.
- With this algorithm positive (for superiority) or negative (for inferiority) rating points are calculated based on the assessment of the therapeutic benefit and the risk profile of the drug of interest versus its comparator in a specific indication [1].
- The evaluation follows an algorithm considering the clinical relevance of the outcomes, the strength of the therapeutic effect and the number of RCTs performed. Furthermore the number and severity of adverse effects as well as therapy interactions are considered in order to calculate an overall benefit/risk score ranging between -25.0 (worst case) and +25.0 (best case) [1].
- In order to identify a systematic approach for the prediction of GBA assessments the algorithms of the EVITA approach were applied to 5 recently published GBA decisions: abiraterone acetate, boceprevir, cabazitaxel, eribulin and telaprevir.
- An overall score was calculated on the basis of the relevant study profiles and outcomes of each selected pharmaceutical, and compared with the published GBA decision.

Underlying Data

- Table 1 shows the active ingredient, the ATC code, the trade name, the indication, the therapeutic standard (comparator) and the data sources for abiraterone acetate, boceprevir, cabazitaxel, eribulin and telaprevir.
- The related information and the resulting efficacy scores are presented in Table 2 for all selected pharmaceuticals.

Table 1: General Information about the selected pharmaceuticals

Active Substance	ATC Code	Trade Name	Indication	Therapeutic Standard	Data Sources
Abiraterone acetate	ATC L02BX03	Zytiga®	Prostate cancer (second line)	Docetaxel & Prednisolone, Prednisolone; BSC*	EMA SPC [2]; Phase III RCT [3]
Boceprevir	ATC J05AE12	Victrelis®	Chronic hepatitis C (treatment naïve)	Peginterferon plus Ribavirin	EMA SPC [4]; Phase III RCT [5]
Cabazitaxel	ATC L01CD04	Jevtana®	Prostate cancer (second line)	Docetaxel & Prednisolone, Prednisolone; BSC*	EMA SPC [6]; Phase III RCT [7]
Eribulin	ATC L01XX41	Halaven®	Breast Cancer (third line)	Capecitabin, 5-Fluorouracil, Vinorelbin	EMA SPC [8]; Phase III RCT [9]
Telaprevir	ATC J05AE11	Incivo®	Chronic hepatitis C (treatment naïve)	Peginterferon plus Ribavirin	EMA SPC [10]; Phase III RCT [11]

*BSC (best supportive care) is only adequate for patients not eligible for docetaxel retreatment; **focus is set on treatment-naïve patients

Table 2: Efficacy score assessment

Active Substance	Primary Endpoint	Number of RCTs	Comparator	Absolute RR	Efficacy Score
Abiraterone acetate	Overall survival (patient relevant)	1	Prednisolone	13%	7.5
Boceprevir	Virologic response (patient relevant)	1	Peginterferon & ribavirin	26%	7.5
Cabazitaxel	Overall survival (patient relevant)	1	Mitoxantrone (BSC)	12%	7.5
Eribulin	Overall survival (patient relevant)	1	Treatment of physician's choice	4%	5.0
Telaprevir	Virologic response (patient relevant)	1	Placebo & ribavirin & peginterferon	31%	10.0

RCTs = randomized controlled trials; RR = risk reduction

- The EVITA risk score of an investigational drug is based on information about adverse events (AE) and AE interactions. The AE profile of a drug is scored on the basis of frequency and severity by considering the highest occurrence of AEs in each of three severity groups:
  - Grades 4 and 5 (disabling AE, life-threatening AE, or death related to AE)
  - Grade 3 (severe and undesirable AE)
  - Grades 1 and 2 (mild AE or moderate AE) according to the Common Terminology Criteria for Adverse Events
- Furthermore AE interactions are a potential source of risk which can emanate from a drug, hence they are taken into account as part of the safety profile assessment as shown in Table 3.

Table 3: Safety score assessment

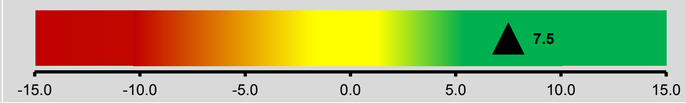
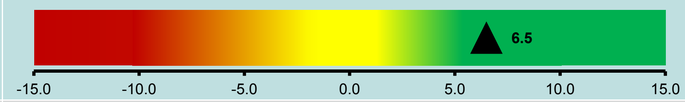
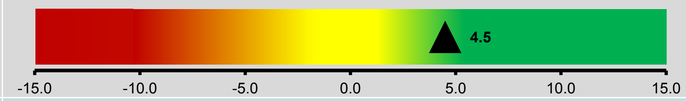
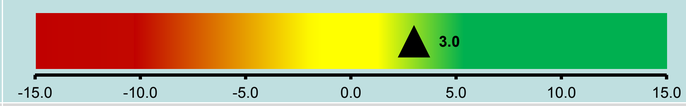
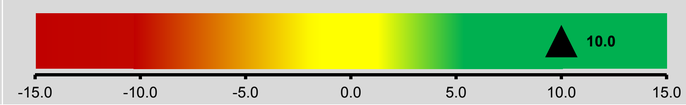
Active Substance	AEs Grade 5&4		AEs Grade 3		AEs Grade 2&1		AE Interactions		Safety Score
	NT	CP	NT	CP	NT	CP	NT	CP	
Abiraterone acetate	≥ 0.1%	≥ 0.1%	≥ 1%	≥ 1%	≥ 1.5%	≥ 1.5%	NS	NS	0.0
Boceprevir	≥ 10%	≥ 1%	≥ 10%	≥ 10%	≥ 10%	≥ 10%	NS	NS	-1.0
Cabazitaxel	≥ 10%	≥ 10%	≥ 10%	≥ 10%	≥ 10%	≥ 10%	Yes*	No	-3.0
Eribulin	≥ 10%	≥ 1%	≥ 10%	≥ 10%	≥ 10%	≥ 10%	Yes**	No	-2.0
Telaprevir	NS	NS	≥ 1%	≥ 1%	NS	NS	Yes**	Yes**	0.0

AE = Adverse Effects; NT = New Therapy; CP = Comparator; NS = Not Stated; *frequent or serious clinical consequences and dosage change; ** dosage change

Results

- The final stage of the benefit/risk evaluation consists of adding up the efficacy and the risk score, both of which are evaluated in comparison to the established therapy, to obtain an overall score.
- According to Puentmann et al "values considerably above zero indicate a likely potential that the new drug features a clinically relevant improvement in treatment and values around zero indicate an ambiguous state which might be clarified by further clinical trials" [1].
- In order to investigate whether the resulting score from utilizing the EVITA algorithm might be a mean for the prediction of GBA decisions on AMNOG early benefit assessments, the calculated overall scores were compared with the published GBA decision on the additional benefit level (Table 4).

Table 4: Benefit/risk assessment results compared to GBA decisions

Active Substance	Overall Benefit/Risk Score	GBA Decision
Abiraterone acetate		Significant Additional Benefit [12]
Boceprevir		Minor to significant additional benefit [13]
Cabazitaxel		Minor Additional Benefit [14]
Eribulin		Minor Additional Benefit [15]
Telaprevir		Minor to significant additional benefit [16]

- As shown in Table 4, the assessments for abiraterone acetate (prostate cancer; GBA decision: significant additional benefit; benefit/risk score: 7.5), boceprevir (hepatitis C; minor to significant additional benefit, 6.5), cabazitaxel (prostate cancer; minor additional benefit, 4.5), eribulin (breast cancer; minor additional benefit, 3), and telaprevir (hepatitis C; minor to significant additional benefit, 10) delivered evidence that there is a correlation between the overall benefit/risk score and the GBA decision.

Discussion

- Although the benefit/risk assessment follows predefined algorithms there are some limitations to be addressed.
- There are situations in which no score could be calculated:
  - As initial step of an assessment of a new drug's potential therapeutic advantage the conditions which must be met for the RCTs to be included in the evaluation process are assessed.
  - If these conditions are not met (e.g. study population does not match the indication; the new therapy has not been compared to the therapeutic standard or versus placebo in the RCT although there is an adequate drug therapy available) the calculation of an overall score is not possible.
- Furthermore, specific data might not be published adequately and comprehensively enough to be directly used for the benefit/risk assessment:
  - This includes the rating of the primary outcome (patient relevant or surrogate parameter), the decision on whether the selected RCT comparator is adequate, and the availability of the efficacy parameter – absolute risk reduction.
  - Furthermore the availability of AE data categorized into the required severity grades and information on AE interactions might not be published in the required detail.
- In all these cases specific assumptions need to applied that can have an effect on the overall score:
  - In cases where there is already a GBA decision published much of these required information can be obtained by screening the GBA documents but if a benefit/risk assessment will be performed in order to predict the possible outcome of an AMNOG early benefit assessment specific assumptions might be necessary and determined via a specific advisory board.
  - Additionally, scenario analyses could help to estimate a 'best case' and a 'worst-case' on the basis of the available data, and thus provide a range for the predicted score.

Conclusions

- Assessment of the potential therapeutic advantage of a new drug by applying the EVITA algorithms appears to be a feasible approach to predict GBA decisions related to AMNOG early benefit assessments systematically.
- However, our number of evaluations is currently limited and further comparisons of benefit/risk scores and related GBA early benefit decisions are to be performed in order to determine the predictive power of the above described assessment approach more precisely.

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