Objective: As of 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 assessment by the joint federal committee (G-BA) which determines one of six additional benefit levels. According to AMNOG any specification of the reimbursement price shall be based on the outcomes of the early benefit assessment. Hence, this assessment serves as a key marker for market access of a new drug in Germany, which poses the question whether it is possible to predict the level of additional benefit that will be established by the G-BA.

Methods: In order to evaluate a possible predictor of G-BA decisions, the evaluation of pharmaceutical innovations (EVITA) score was calculated and retrospectively compared with 40 published G-BA decisions. The EVITA algorithms evaluate a new comparator for an indication and in relation to a relevant comparator on the basis of randomized controlled trial (RCT) evidence. EVITA translates the RCT outcomes on the therapeutic benefit and risk profile into rating points, which are expressed as a total EVITA score.

Results: Univariate ordinary least squares and ordered logit regression analyses show statistically significant correlations between EVITA score and the G-BA additional benefit level. Moreover, for the prediction of an additional benefit level of at least ‘minor’, an EVITA score cutpoint of 3 is associated with a sensitivity of 100% and a specificity of 80%. For the prediction of an additional benefit level of at least ‘considerable’, an EVITA score cutpoint of 7.5 is associated with a sensitivity of 100% and a specificity of 93.1%.

Conclusions: The present investigation indicates that the EVITA score may have the potential for the prediction of G-BA decisions related to AMNOG early benefit assessments.

Introduction

On 1st January 2011 the German act on the reform of the market for medicinal products became effective [1].

Due to this act the means of obtaining cost reimbursement for pharmaceuticals from the German statutory health insurance (GKV) are significantly changed. New drugs entering the market, which are a result of active research and innovation in the German pharmaceutical market (AMNOG) became effective [1].

Since then the normal procedure for reimbursement of a new pharmaceutical is an early assessment by the joint federal committee (G-BA) which determines the benefit profile and the outcomes of randomized controlled trials (RCT) evidence. EVITA translates the RCT outcomes on the therapeutic benefit and risk profile into rating points, which are expressed as a total EVITA score.

Materials and Methods

Using the EVITA approach [2], developed by the University of Bremen, we investigated whether the level of benefit predicted by the EVITA score can be used to predict the level established by the G-BA.

The EVITA algorithm evaluates a new compound for a given indication and in relation to a relevant comparator on the basis of randomized controlled trial (RCT) evidence. EVITA translates the RCT outcomes on the therapeutic benefit and risk profile into rating points, which are expressed as an efficacy score and a safety score, respectively.

The combined EVITA total score (efficacy score plus safety score) ranges theoretically from a minimum of -25 to a maximum of +25 but most results are expected to be located between the range of -5 to +10 [2].

In order to evaluate the EVITA score as possible predictor of G-BA decisions, the algorithms of the EVITA approach were applied to 40 G-BA decisions (85% of the total) that were finalized by the end of December 2013. For all AMNOG cases included in our analysis the documents provided by the G-BA have been used as central data source for extracting all relevant information to populate the EVITA algorithms [2].

Looking at these forty assessments the G-BA determined the following additional benefit levels: no additional benefit (n=7), non-quantifiable additional benefit (n=9), very low additional benefit (n=5), low additional benefit (n=4), moderate additional benefit (n=7), considerable additional benefit (n=3), and high additional benefit (n=2). In the present study, the EVITA score was used to predict the level of additional benefit established by the G-BA, as reported by the joint federal committee (G-BA) in its decision).

In a next step, two regression models were applied to outline the relationship between EVITA scores and G-BA decisions. Therefore, the EVITA scores of the 40 G-BA decisions were transferred to numerical values according to the different benefit categories (no additional benefit: 0; non-quantifiable additional benefit: 1; very low additional benefit: 2; considerable additional benefit: 3; and high additional benefit: 4). A stepwise regression analysis was performed to establish which variables have a significant impact on the level of additional benefit established by the G-BA.

First, sensitivity and specificity values are discussed for different cutpoints. The sensitivity may be described as the true positive results divided by the sum of the true positive and the false negative results. The specificity is defined as the true negative results divided by the sum of the true negative and the false positive results. Furthermore, a Receiver Operating Characteristic (ROC) curve was generated.

As shown in figure 1, there are two substances where the G-BA benefit level and EVITA score results do not fit well together: bosentan and telaprevir. This discrepancy might be based on the issue that within the AMNOG assessment the primary endpoints of the underlying RCTs were considered as patient-relevant although the IQWiG rated them as surrogate parameters. The EVITA scores were calculated by rating these endpoints as patient relevant. If one would, however, consider the primary endpoints as surrogate, the EVITA scores would decline to 2.8 for bosentan and to 5.0 for telaprevir. This would lead to an increase in the separability of the data and the specificity of the above discussed EVITA score cutpoints for predicted G-BA benefit levels of at least ‘minor’ (EVITA score ≥ 3) and at least ‘considerable’ (EVITA score ≥ 7.5) would increase to 97.5% and 96.6 %, respectively.

According to an assessment of Ruof et al. 2012 there have been some situations observed where the G-BA was not following the IQWiG recommendation: in fact the G-BA assigned a higher rating in four cases [3]. Such decisions are most likely triggered by additional arguments and additionally submitted data provided to the G-BA during the communication phase of the early benefit assessment. Such proceeding might lead to the case that the additional benefit level predicted by applying the EVITA algorithms might be underestimated (compared to the real-world G-BA decision).

Discussion

As shown in figure 1, there were twenty G-BA decisions that have not been included in our assessment as the G-BA has determined the ‘no additional benefit’ level due to procedural errors. The key reasons for a procedural error related ‘no additional benefit’ rating was based on the fact that the manufacturer submission was either missing (n=4), incomplete (n=2), focused on the wrong comparator (n=2) or on the wrong patient population (n=2). There are no well-defined criteria of a G-BA submission that will in the future lead to a procedural error related ‘no additional benefit’ rating by the G-BA.

Beside these limitations the presented approach to potentially predict G-BA additional benefit levels is regarded as a useful tool for the pharmaceutical industry in order to rate the success chances of their product for gaining an adequate reimbursement by the National Association of SHF Funds in Germany.

Conclusions

Although there are some limitations to be considered, especially the limited size of our sample of forty G-BA decisions and the retrospective character of the analysis, an assessment of the potential therapeutic advantage of a new drug by applying the EVITA algorithms may have the potential to act as a predictor of G-BA decisions related to AMNOG early benefit assessments.