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# From evidence assessments to coverage decisions? The case example of glinides in Germany

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### ABSTRACT

In Germany, coverage decisions in the statutory health insurance (SHI) system are based on the principles of evidence-based medicine. Recently, an evidence assessment by the Institute for Quality and Efficiency in Health Care (IQWiG) of the oral antidiabetics of the glinide class showed that their long-term benefit is not proven. Accordingly, the responsible Federal Joint Committee (G-BA) decided to exclude glinides from prescription in the SHI system. This was, however, objected to by the Ministry of Health, which is charged with legal supervision. We use this case to illustrate the path from evidence assessments to coverage decisions in Germany against the background of the latest health reform, which has changed the legal requirements for evidence assessments and the ensuing coverage decisions.

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## 1. Political and economic background

In Germany, about 85% of the population is covered by statutory health insurance (SHI), a mandatory social insurance system [1]. The regulation of the system has been devolved by the government to self-governing corporatist bodies of both the sickness funds and the medical providers' associations [2].

With health care reform coming into effect in 2004, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) was established as the supreme decision-making body that, among other responsibilities, determines the benefit package and thus superseded the Federal Committee of Physicians and Sickness Funds, which had been the most important body for benefit assessments and coverage decisions since 1923 [3,4]. The G-BA comprises

physicians (Kassenärztliche Bundesvereinigung [Federal Association of SHI Physicians]), dentists (Kassenzahnärztliche Bundesvereinigung [Federal Association of SHI Dentists]), hospitals (Deutsche Krankenhausgesellschaft [German Hospital Federation]), sickness funds (GKV-Spitzenverband [Federal Association of Sickness Funds]) and patients [3]. It has the authority to issue directives that are directly binding for the health system and thus all those acting within it [5]. While the G-BA is not a subordinate agency and is independent of the Federal Ministry of Health (Bundesministerium für Gesundheit [BMG]), the Ministry exercises legal supervision over it. As such it may object within a period of two months to the G-BA's coverage decisions coming into effect on the basis of legal (not factual) reasons, and it approves the G-BA's Code of Procedure, which regulates methodological and procedural requirements for evaluations serving as the basis of directives [5] (see Fig. 1).

To inform the G-BA's coverage decisions, in 2004 the legislator also created the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) as a non-government, non-profit institute [4]. One of its main tasks is to produce

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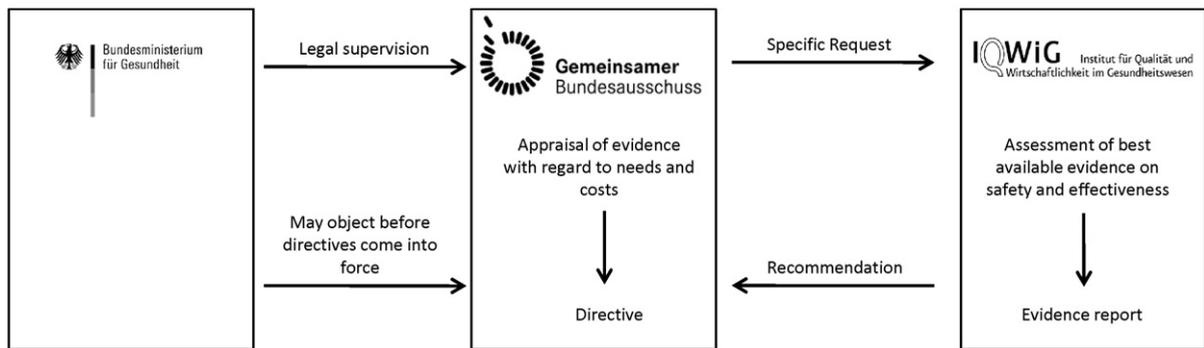


Fig. 1. Interplay of Federal Ministry of Health, G-BA and IQWiG (adapted from [7]).

evidence-based reports on drugs, non-drug interventions, and diagnostic and screening methods for the G-BA [6]. IQWiG forwards its results as recommendations to the G-BA, which must take them into account in its decision-making process (§139b,4 SGB V).

The German Social Code Book (Sozialgesetzbuch, SGB) lays out the general criteria that services of the benefit package have to comply with. All SHI members are entitled to services that are adequate, expedient and cost-effective, and do not exceed what is necessary (§12,1 SGB V). The therapeutic benefit of services has to be in accordance with the generally accepted state of medical knowledge (§2,1 SGB V) (see also [8]). As opposed to the other criteria, the term “expediency” is not used in decision-making in other countries; in general, a service is “expedient” if it can be expected to achieve a specified therapeutic aim [9]. However, it has been pointed out that the concept creates considerable ambiguity, especially in relation to the term “benefit” [9].

## 2. Characteristics of this policy

Drugs are available to all SHI insured immediately after their approval by the drug regulation authority (i.e., the European Medicines Agency or the Federal Institute for Pharmaceuticals and Medical Devices) [10]. Since its inception, the G-BA has been commissioning IQWiG to conduct evidence assessments of drugs that were already on the market, but where there were doubts concerning their (comparative) benefit with regard to patient-relevant outcomes. In the absence of a fourth hurdle, which would require an independent assessment before new drugs were reimbursed, the main regulatory mechanisms available to the G-BA have been the formation of reference price groups, which define the reimbursement ceiling for a group of comparable drugs, the preparation of therapeutic advice on cost-effective prescription, and restrictions and exclusions from prescription [10]. Up until the end of 2010, the prescription of drugs (as well as non-drug items and procedures) could be restricted or excluded if, “according to the generally accepted state of medical knowledge, the therapeutic benefit, the medical necessity or the cost-effectiveness has not been demonstrated, if a drug is inexpedient and, in particular, if there are one or more possible treatments of comparable therapeutic benefit, but

more cost-effective” [11] (§92,1 SGB V version valid until December 31st, 2010). Applying this principle and based on IQWiG assessments, the G-BA has restricted the prescription of drugs over recent years.<sup>2</sup> In particular, the decision to restrict long-acting (glargine, detemir) and short-acting insulin analogues (aspart, glulisine and lispro) for type 2 diabetes as long as higher costs are involved caused considerable protest from manufacturers and patients, and the G-BA was unsuccessfully sued several times [12].

However, the legal basis for excluding or restricting drugs was changed significantly with the latest health reform, passed in November 2010 (Arzneimittelmarktneuordnungsgesetz, AMNOG [Act to Reorganize the Pharmaceutical Market in the SHI]), with considerable impact on future coverage decisions. Generally, the new legislation introduced a shift in terms of regulatory mechanisms from exclusions and restrictions to price negotiations [13]: since 2011, so-called “early benefit assessments” have been carried out for all newly approved drugs. Within three months of a drug’s market access, the IQWiG performs such assessments based on dossiers submitted by the industry (as opposed to carrying out a comprehensive search for relevant literature itself) to investigate whether a new drug has an “additional benefit” compared to a specific comparator set forth by the G-BA [14]. On the basis of these assessments and following hearings with experts and the drug manufacturer, the G-BA either decides that a drug has no additional benefit and includes this drug in the reference pricing system [15] whenever possible. If, on the other hand, that is not possible or if the G-BA comes to the decision that a new drug indeed has an additional therapeutic benefit, the Federal Association of Statutory Health Insurance Funds and the respective pharmaceutical company will enter price negotiations [16]. In case of no additional benefit, the reimbursement will then be limited to the price of the appropriate comparator.

For those drugs already on the market, however, the new legislation set up a much higher hurdle for exclusion by shifting the burden of proof regarding the (lack of) benefit from manufacturers to the G-BA [17]: As of January 1,

<sup>2</sup> All directives on drugs made by the G-BA are accessible in German online: [www.g-ba.de/informationen/beschluesse/zum-unterschied/2/](http://www.g-ba.de/informationen/beschluesse/zum-unterschied/2/).

2011, the G-BA itself is required to demonstrate that a drug is “inexpedient” (§92,1 SGB V version in effect since January 1st, 2011).

When the plans for this change in legislation became public in late summer 2010, the widespread interpretation was that a lack of studies demonstrating a benefit will no longer be sufficient to restrict or exclude a drug. This was highly criticized by the scientific community on the basis of strong methodological concerns [18]. While the regulation was nevertheless included in the final version of the law, it was supplemented by granting the G-BA the right to request studies from manufacturers within three years if proof of benefit is lacking. If the manufacturer does not provide the necessary studies in time, the G-BA then has the authority to exclude the respective drug from prescription (§92,2a SGB V).

The first time that this new policy was applied was in the case of glinides. We therefore use the example of glinides to illustrate the interplay between the IQWiG, the G-BA and the Ministry, and the implications of the change in legislation.

### 3. Process analysis using the example of glinides

The G-BA commissioned the IQWiG to assess the evidence of drug and non-drug interventions for treating widespread medical conditions including diabetes mellitus type 1 and 2 in February 2005 [19]. Among the interventions assessed were glinides (repaglinide and nateglinide) for type 2 diabetes. A draft review protocol setting out the methods for the evidence report was made available for public comment by the IQWiG in 2007 to provide stakeholders the opportunity for input [20]. On the basis of the methods specified, the IQWiG published its draft report in December 2008 [21], again with the opportunity for the public to comment on it within four weeks. The final report was published on June 4, 2009 [22].

The researchers assessed the evidence of the long-term benefit of glinides for patient-relevant outcomes by comparing repaglinide and nateglinide to placebo or no treatment and to another glucose-lowering drug or non-drug treatment as well as to each other [23]. They searched for randomized controlled trials lasting at least 24 weeks in electronic databases, secondary publications, clinical trial registries, and publicly accessible drug approval documents. The relevant manufacturers were asked to provide relevant information on published and unpublished studies. Eight relevant studies were identified for repaglinide and two for nateglinide. However, as the treatment duration in the studies was 24 weeks to 14 months, none of them sought to investigate the long-term benefits of glinides. From the available trials, no conclusions were possible on the effect on important patient-relevant outcomes [24]: Several outcomes (e.g., avoidance of late complications, health-related quality of life and patient satisfaction) were not investigated at all in the studies, for other outcomes data were not presented with sufficient transparency, and trials were susceptible to bias [23,24]. On the basis of the evidence identified, the researchers concluded that “the benefit of glinides in the treatment of type 2 diabetes is not scientifically proven. Nor do they perform better than

other antidiabetics available in tablet form, such as metformin and sulfonylureas. As a result, there is also no proof of additional benefit” [24].

The G-BA formally approved the IQWiG’s assessment and subsequently started a consultation with stakeholders (see Fig. 2). On June 17, 2010, about a year after the publication of the IQWiG’s assessment, the G-BA decided to generally exclude glinides from prescription, except in the case of patients with severe kidney malfunction for whom repaglinide, as a monotherapy is the only option for orally reducing glucose levels [25]. The G-BA justified this decision with reference to the IQWiG’s conclusions that proof of benefit was lacking, because there were no relevant studies for the predefined patient-relevant outcomes or available data were insufficient, and that there was no proof of additional benefit compared to other therapy options [26].

After the publication of the decision, an exchange of letters between the Ministry and the G-BA began, in which the Ministry asked for further justification of several aspects and thereby postponed the two-month objection period.<sup>3</sup> During this time, the new legislation was passed and had already come into effect when the Ministry finally objected to the decision in February 2011 (see Fig. 2). By law, the G-BA is guaranteed the right to file a law case against an objection by the Ministry within one month and it made use of this right in the case of glinides, mainly in order to comply with the time limit [27].

The discussion between the G-BA and Ministry culminated in the question as to whether the G-BA had demonstrated that glinides are “inexpedient” in terms of the new legislation. The G-BA used the following line of argument: as proof of the benefit of glinides for patient-relevant outcomes is lacking and as the benefit is better documented for other drugs by relevant studies, glinides are inferior in this respect and therefore not an expedient therapy option – hence inexpedient (Letter from December 2, 2010). The Ministry, however, did not accept this interpretation: in its objection it pointed out that the fact that studies are available for other drugs but lacking for glinides is not sufficient as proof of inexpediency. Instead, it suggested that glinides would have to be proven to be inferior compared to alternative drugs in appropriate studies in order to be declared inexpedient (Letter from February 21, 2011).

### 4. Expected outcome

The new legislation determined that from now on, only proof of inexpediency can justify the exclusion or restriction of a drug. However, the legislation itself is not explicit as to how “inexpediency” is defined and the case of glinides suggests that the concept is currently interpreted in different ways by the G-BA and the Ministry. The G-BA is planning to develop criteria to determine “expediency” and “inexpediency” in a new version of its Code of Procedure. Since the Code has to be approved by the Ministry, this may provide an opportunity for a conceptual clarification of the

<sup>3</sup> All letters are accessible in the German language via the G-BA website <http://www.g-ba.de/informationen/beschluesse/1142/>.

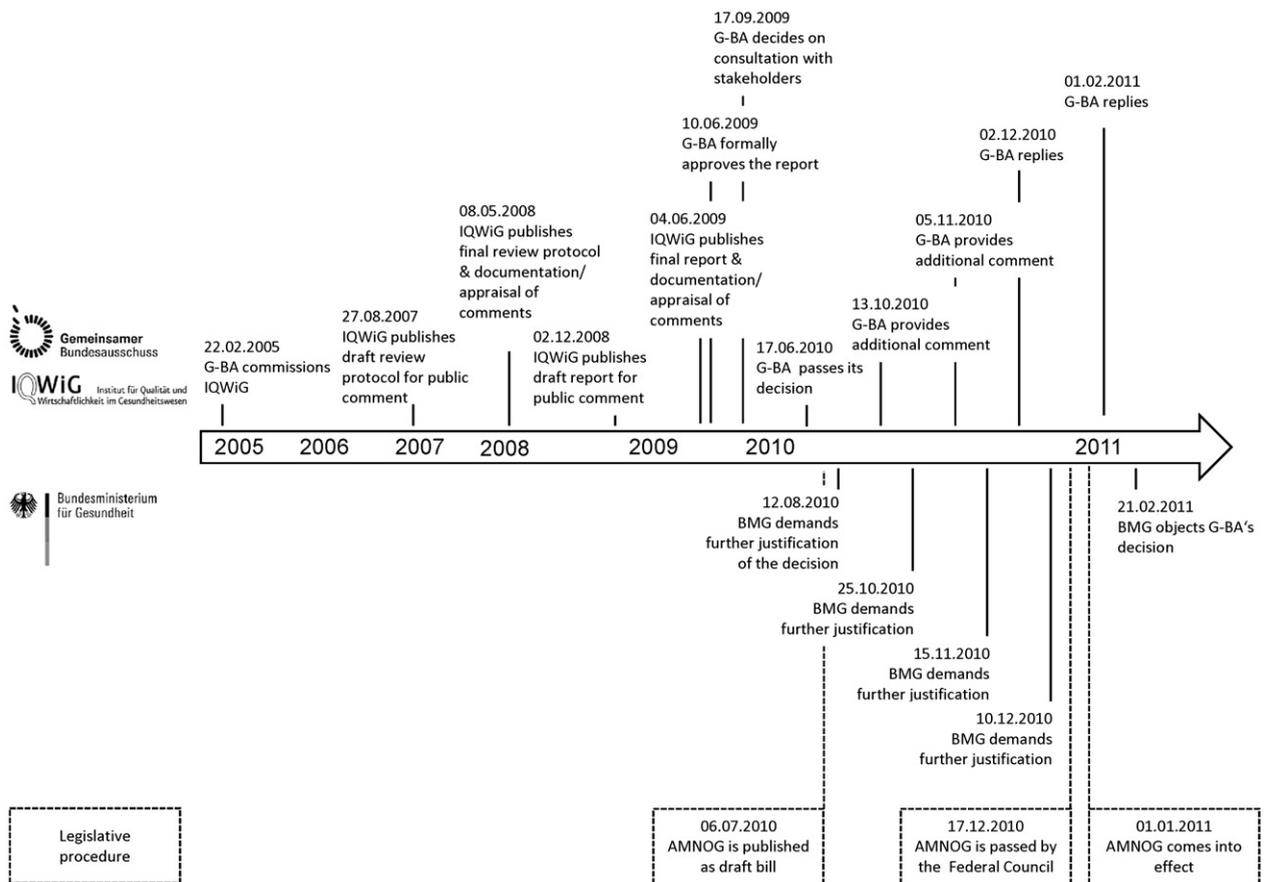


Fig. 2. Significant points in the process of making a decision on glinides for type 2 diabetes.

term between the two parties. If the Ministry enforces its current position (see also [28]), essentially two scenarios will remain in which a drug can in future be excluded on the basis of inexpediency: first, if the G-BA or an assessment carried out by the IQWiG demonstrates on the basis of relevant studies that a drug is inferior to a comparable therapy option. This was the case, for example, with the assessment of the antidepressant reboxetine, which was shown to be inferior to selective serotonin reuptake inhibitors and excluded from prescription by the G-BA without objection by the Ministry of Health [29]. In the second scenario in which – as in the case of glinides – studies demonstrating a benefit are lacking, a second step will be necessary, namely a request from the G-BA to manufacturers to provide studies which prove the benefit. On a case-by-case basis, an exclusion from prescription is possible after the time limit has expired if the manufacturer has not provided the necessary data.

It has been suggested that traditional, comprehensive evidence reports will become less relevant as a tool for coverage decisions regarding drugs in Germany in the future [13]: not only because new drugs will be assessed in an early benefit assessment directly after their approval, but also because the new regulations for drugs that are already on the market described here diminish the potential impact of the assessments. Generally, the latest health reform

endorses price negotiations as a regulatory mechanism over exclusions and restrictions for the German SHI system.

Similar legislative changes as described above for drugs are currently being planned regarding the exclusion of medical procedures carried out in the hospital sector: A recently (June 2011) published draft bill foresees that the G-BA shall no longer be able to restrict these procedures on the basis that evidence for their benefit is lacking. Instead, the draft bill suggests that only if an assessment demonstrates that a procedure does not have “potential” as a treatment option (particularly because it has clearly been shown to be ineffective or even harmful) it may be excluded from coverage by the SHI [30]. On the other hand, however, the G-BA will have more powerful instruments to initiate and finance studies for evidence generation. The new law is planned to come into effect on January 1, 2012.

### Competing interests

JK is employed by IQWiG.

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