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The German AMNOG and its current potential implications on the Spanish and Belgian pricing and reimbursement decisions

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ABSTRACT

Background: EU policymakers have implemented mechanisms to slow down the rate of increase in health care costs. The most recent reform that came into effect in Germany was the Act to Reorganise the Pharmaceutical Market (AMNOG - Das Arzneimittelmarktneuordnungsgesetz).

Methods: Exemplarily for countries, which used Germany as a price reference country, Spain and Belgium were chosen for pilot evaluation if AMNOG might have any further impact on reimbursement and pricing decisions in these countries. The general market access and potential impacts on clinical development programs will be discussed and evaluated.

Results: In Spain, GBA assessments may influence the central decisions in pricing and reimbursement in the sense that lower prices will be expected for new drugs in the benchmarking process. In Belgium, AMNOG will also have an impact: the Price Commission will possibly observe lower prices than before, what may lead to other decisions for approved Belgian prices. More importantly, the decisions in Germany, related to added benefits of new drugs, might influence the Commission members.
Finally, clinical developments of new compounds may also be influenced by AMNOG, regarding the requests of reimbursement decision makers for special clinical trial designs.

Conclusions: The potential impact on additional clinical benefits and price decisions with the Spitzenverband der Krankenkassen may be observed in some other countries as well. Furthermore, the impact on future clinical development programs of new compounds might as well be significant. Further research and experience in Germany and other countries is needed and awaited.

INTRODUCTION: HEALTH CARE REFORMS AND AMNOG

In recent years, the introduction of new innovative medicinal products has become increasingly challenging in result of budget pressures, the introduction of more complicated listing procedures and higher demands on the added value of medicinal products and other therapies. For the most part, policy measures have relied on budgeting or price controls, including negotiated

prospective budgets for hospitals, centralized negotiated budgets for outpatient physicians, including drug prescriptions, and limitations on payments for particular medications. The autonomous behaviors of prescribers have been restricted and controlled by national clinical guidelines, local formularies and/or local agreements between prescribers and health insurers, who sanction for deviant prescription behaviors or reward "proper" adherence to the rules. Although each country in Europe has its own specific cost containment measures and restrictions for market access, the above-mentioned changes have a similar impact on each new medicinal product, introduced in Europe: summerised as an increasing number of refusals and restricted access to new therapies, following negative reimbursement decisions. Because those traditional central cost containment measures were only partially successful, due to a potential lack of incentives, the health authorities in Europe started developing and implementing incentives for efficient health care delivery. Despite considerable differences among various European countries, there are two related and commonly observed trends: implementation of market-mimicking mechanisms and decentralisation of health care decision-making process. The key aim of these reforms is to control increasing health care costs, which has become an important part in the overall expenditure for social care.

IN RECENT YEARS, THE INTRODUCTION OF NEW INNOVATIVE MEDICINAL PRODUCTS HAS BECOME INCREASINGLY CHALLENGING IN RESULTOF BUDGET PRESSURES, THE INTRODUCTION OF MORE COMPLICATED LISTING PROCEDURES AND HIGHER DEMANDS ON THE ADDED VALUE OF MEDICINAL PRODUCTS AND OTHER THERAPIES

Governments and policymakers of EU member states have, over the last decade, implemented a series of mechanisms and reforms to slow down the rate of increase in health care costs. The most recent reform, that has come into effect in Germany, is the Act to Reorganise the Pharmaceutical Market (AMNOG), which has changed Germany's traditional status of their market, known as a "fast-entry and premium-priced" trading environment. With the new reform in place, the pharmaceutical manufacturers are now required to show not only the benefits from their new drug vs. placebo, but also to unveil any additional benefits from their new medicinal products over and above appropriate therapeutic alternatives. According to the Federal Ministry of Health (MoH), the extent of additional benefits from a new drug will be classified in one of the following categories:

1. Remarkable additional benefit;
2. Considerable additional benefit;
3. Minor additional benefit;
4. Additional benefit not quantifiable;
5. No evidence for additional benefit;
6. Less benefit than from a comparable product.

At the time of market access, a manufacturer has to submit a 'benefit dossier' to the Federal Joint Committee (Gemeinsamer Bundasausschuss, G-BA) for assessment. The dossier must specify the conducted studies, information on tested medical indications, therapeutic benefits, additional benefits in comparison to alternative treatments, the cost of therapy and the expected expenses of the therapy for the SHI, the estimated number of patients or patient groups expected to benefit from the new drug and special requirements in place to assure compliance and adherence of patients, prescribed the drug to be used. The G-BA, the Institute for Quality and Efficiency in Healthcare (IQWiG;Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) or third parties commissioned by the G-BA should assess and publish the dossier within three months. Over the following three months, the manufacturer will have an opportunity to comment during an organised hearing. During this time, the G-BA will reach a final decision on additional benefits, based on the results of the assessment (additional benefit/no additional benefit). If no additional benefit for a drug can be demonstrated, it will be classified

directly into a reference-price group. If no reference price group exists, this new drug will be discounted to set the reimbursement price no higher than that of a relevant comparable product. If the new drug is considered to show an additional benefit, then its price will be negotiated in centralised contracts between the Head Association of the SHI funds (GKV-SV) and the manufacturer, according to § 130b SGB V 1. The negotiated price should be as high as that of the comparable product, plus a mark-up reflecting the additional benefit; and it will the be binding for all German SHI as well as for private health funds. This new price will be effective after thirteen months from market launch of the new drug. Should an agreement fail to be reached within one year, an arbitration body will decide on a rebate, based on an international reference price. If this negotiated price is not accepted (by either party), both the manufacturer and the SHI can ask for a cost-effectiveness analysis (CEA) to be undertaken by IQWiG with perspective of determination of a CEA-based price (which would then become applicable retrospectively from the start of month 13). If price negotiations bring a lower reimbursement price for the SHI, the official list prices will not change. Therefore, other European countries cannot take advantage of lower list prices for their negotiations.

HISTORICAL DEVELOPMENT: GERMANY AS A PRICE-REFERENCE COUNTRY FOR OTHER COUNTRIES

It has been speculated that the implications of AMNOG on the pharmaceutical market will be significant. AMNOG may not only have significant impacts on drug prices in Germany, but may also be reflected in international drug prices. German drug prices influence – directly or indirectly, formally or informally – the international drug reference prices in19 countries, including: Austria, Belgium, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Romania, Slovakia, Slovenia, Spain and Switzerland. The countries, which do not refer to German prices, include: Bulgaria, Croatia, Denmark, Lithuania, Poland, Portugal, Sweden, and the UK. Out of all European (here: EU-27) countries, only UK, Sweden, Germany, and Denmark do not currently have an external price referencing policy. In Denmark, this policy has been discontinued since 2005. In Sweden, external referencing was ceased in 2002. The factor of external reference pricing is already affecting the path of product launches in Europe. For example, Boehringer-Ingelheim and Lilly ceased launching their type II diabetes drug, linagliptin(Trajenta®), for fear of negative pricing prospects for the product.

SUMMARY OF FIRST ASSESSMENTS AND PRICING NEGOTIATIONS WITHIN AMNOG

Within the first 28 months, up to April 2013, dossiers for more than 50 pharmaceutical specialties have been submitted to the G-BA. The results of benefit assessments so far: 35 assessments completed, six close to be finished, and seven have just started. Three pharmaceuticals were exempted from the early benefit assessment for an insignificant budget impact for the statutory health insurance in Germany and one has no status.

Comparing the manufacturer's dossiers, the benefit assessment of the IQWIG and the final resolutions, published by the G-BA, striking is the difference, regarding the estimation of potential innovations and additional benefits in comparison to standard therapy. Only for some drugs was the manufacturer's positive estimation fully approved by the IQWIG or the G-BA. For some pharmaceuticals, assessed for several indications, the evaluation has provided different results for different indications, ranging, e.g., from „significant additional benefit" in one indication to „no additional benefit" in another (e.g. Ticagrelor) .

For the 35 pharmaceuticals, so far finally assessed, the results are as follows: 13 have no proven additional benefit, which means the G-BA has to check whether they could

be allocated to the existing reference price group or whether a new reference price group could be formed. If a drug with no additional benefit cannot be allocated to any reference price group, the GKV-Spitzenverband (National Association of Statutory Health Insurance Funds) and the pharmaceutical company have to negotiate a rebate, resulting in annual treatment costs not higher

than those for appropriate comparable product. Three products do not have any quantifiable benefit, 13 reveal marginal and six fairly significant additional benefit. Five products have been regarded to be pharmaceuticals for the treatment of a rare disease in accordance with EC regulation (No. 141/2000 / orphan drugs) and, therefore, the additional medical benefit is said to have been proven through market authorization. For these pharmaceuticals, the rebate on the list price has already been or still has to be negotiated between the manufacturer and the GKV-Spitzenverband. Two drugs have directly been allocated to a reference price group.

Some pharmaceuticals have already re-entered the assessment process for a second time. The very short period for the re-entry is due to the fact that the assessment procedure is new to all parties involved. In case the additional benefit could not be proven because of missing evidence persuant to article 35a paragraph 1 sentence 5 SGB V (Sozialgesetzbuch V / Fifth Book of the German Social Code), the pharmaceutical company was free to submit a new dossier at any time until 31st December 2012. From 1st January 2013, submitting a new dossier for a second

benefit assessment is only possible after one year.

The G-BA has decided to perform a benefit assessment for the three DPP-4-inhibitors (sitagliptin, vildagliptin and saxagliptin). This is for the first time that pharmaceuticals from the established market have to prove their additional benefit in comparison to standard therapy. On April 18th 2013, the G-BA published criteria for the benefit assessment for drugs of the established market and defined the drugs to be assessed. So far, six pharmaceuticals or groups of pharmaceuticals – namely for severe pain, osteoporosis, the prevention of stroke for patients with atrial fibrillation, diabetes, depression and rheumatoid arthritis – will be called upon until the end of 2013.

Beside the differences in the estimation of the potential innovation and the additional benefit in comparison to the standard therapy, the major topic of the discussion between the pharmaceutical company on one hand and the G-BA and IQWIG on the other is the definition of the, so-called, „appropriate comparator". In accordance to AMNOG regulations, the manufacturer may suggest a comparator in the dossier, but the final decision is up to the G-BA. As an example, the manufacturer of linagliptin suggested the DPP-4-inhibitor sitagliptin as an appropriate comparator, whereas the G-BA decided to compare with the combination of sulfonylurea and metformin. The fear of the manufacturer was evidently such that if a branded drug is compared with generics, the final price will be much lower than if it were compared with another branded drug. Therefore, the pharmaceutical company withdrew linagliptin from the German market after the publication of the G-BA resolution.

The pricing negotiations between several manufacturers and the GKV-Spitzenverband started this year in January with a "noisy" campaign in press media. The major topic of discussion was the group of countries with the reference price. As the negotiating parties could not agree on this question, the arbitration body had to decide about the basket of reference countries. The 15 countries named are Belgium, Denmark, Finland, France, Greece, UK, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Czech Republic and Spain. These 15 countries represent the majority of the EU commercial power and about 80% of the EU population. Due to the fact that they differ in many economical parameters, the discussion is still continued if only countries of comparable GNP should be chosen for comparison.

Despite the on-going discussions, there are first results of the pricing negotiations. Until April 2013, the GKV-Spitzenverband and the manufacturers had negotiated a rebate for 17 pharmaceuticals. For another three pharmaceuticals, the rebate had to be fixed by the arbitration board. Only a few results have been published in detail as press releases on the website of the GKV-Spitzenverband. A list of all the 20 pharmaceuticals, though without any details, has also been published by the GKV-Spitzenverband. A.T.I Arzneimittelinformation Berlin GmbH has published the detailed results for the first 14 drugs at the end of January 2013. With price (P) being only one variable of the total turnover expression (P*Q), there is still a number of volume restrictions, stating that these drugs may only be used within their assessed indications and if "economically appropriate". The GKV-Spitzenverband has published an information on its website, when a prescription for ticagrelor, pirfenidon or abirateron may be justified on the grounds of being a "special feature" of the doctor's office ("Praxisbesonderheit") and may, therefore, be perceived as economically appropriate.

THE PRICING NEGOTIATIONS BETWEEN SEVERAL MANUFACTURERS AND THE GKV-SPITZENVERBAND STARTED THIS YEAR IN JANUARY WITH A "NOISY" CAMPAIGN IN PRESS MEDIA. THE MAJOR TOPIC OF DISCUSSION WAS THE GROUP OF COUNTRIES WITH THE REFERENCE PRICE.

DISCUSSION: A POTENTIAL IMPACT OF AMNOG ON THE EUROPEAN PRICING & REIMBURSEMENT LANDSCAPE

For a globally operating pharmaceutical company, the clinical development program of a (new) compound is essential for that

compound's lifecycle and commercial success. Hence, the study phases and, especially the countries having a significant impact on the study design and implementation, are crucial at every stage of the process. Normally, larger countries with higher business potentials have a larger impact in terms of clinical design decisions (currently especially the US). As the German market is still an important market in terms of business, price-setting, and even potential impact on other (smaller) markets, this could now also change the development side of a (new) compound. For example, the clinical endpoints and comparators of choice could be chosen to satisfy the German standard, and this might then also have an impact on other countries. Or, in the outcomes space, a patient-relevant endpoint (e.g. overall survival in oncology) might be chosen over a surrogate endpoint (e.g. progression-free survival in oncology), as this might increase the chances of success and hence a better price in Germany. Potentially, there might now also be more than a few studies being executed for marketing authorization and market access, dependent on different regions in the world: Europe, with a special focus on Germany and the UK, might have other requirements than the US or Asia.

During the last decade, the common practice of the pharmaceutical companies was targeted to first market new agents in those "free price" countries with high income level, such as Germany, where high prices could be easily fixed without reducing the expected sales and, later on, to apply for similar prices in the remaining countries. If regulators did not agree with requested prices, some companies challenged to withdraw the new agent from that market, claiming that a parallel trading at lower level would reduce their profit margins, which would, in turn, lead to cuts in research and development activities. Hence, negotiations usually ended in a minus 10-15% from the benchmarked original price abroad.

At present (in 2013), in Spain, the new Royal Decree Law (16/2012) consolidates the idea of aligning new products' prices to the lowest existing prices and it also opens a possibility to review prices after a certain period, if, e.g., a new information becomes available. There is still no feedback from these latter activities. Re-evaluation of products in terms of efficacy and price has been possible in Spain during the last 3 decades, since the introduction of the General Act of Health (year 1986), the former Law of Drugs (year 1992) and the newer Act of Drugs (year 2006). However, this re-evaluation has adopted several forms. For instance, during the 1990s and the following decade, there were several price cuts and delistings of drugs from public reimbursement, based on efficacy grounds (at least, it was claimed to be based on those grounds) as well as on the low level of severity of the diseases targeted by those drugs. However, it was believed that a higher budget control promoted those decisions. Other examples of this practice come from the fact that, since new drugs are more effective than the former ones, a review of the prices of those older ones is possible because, in relative terms, they have lost efficacy. Frequently, this review takes place at the hospital level where higher discounts are requested by hospital pharmacies and accepted by manufacturers, without modifying the official price of the agents (that perhaps is also used as benchmark by other countries). Regional directions of pharmacy and regional health technology assessment agencies also review many drugs on terms of effectiveness and safety and produce reports and recommendations regarding their prescription. Based on these reports, regional health authorities may also request discounts, guide the decisions of physicians by writing protocols, and program procurement and/or dispensing software in an effort to constrain electronic prescriptions.

The impact of NICE has been important in this field, given that its reports are public and visible on the web site. Many Spanish health authorities read those reports to better understand the value of new agents and to know the features and concerns around them. This knowledge is integrated in the

decision-making process of both central and regional health authorities. However, GBA assessments are not so influential yet on the decision processes as those coming from NICE, perhaps due to the way they are reported or to its more recent arrival to the arena of the evaluation. However, the new policy to fix prices in Germany will also certainly have some influence on the Spanish central decisions, regarding price and reimbursement in the sense that lower prices will be expected for new drugs in the benchmarking process.

In Belgium, pricing and reimbursement decisions for new drugs are based on several criteria, and the current system is already in place since 2002. If a manufacturer of a new drug claims that this drug has an added therapeutical benefit and requests a price premium, compared to current care, then this new drug is evaluated based on 4 criteria:

1°. the size of the therapeutical added value;
2°. The therapeutical and social need;
3°. The cost-effectiveness and
4°. The impact on the health care budget.

Although these criteria are supposed to be investigated at the same time, in practice, the first question that is systematically asked by the Commission for the Reimbursement of Medicines, is the question about the therapeutical added value.

Only if this added therapeutical benefit is clear and agreed upon by the commission members with 2/3rd majority, the other criteria become relevant.

In the meantime, and initially separate from this reimbursement process, the pricing commission compares the proposed price by the manufacturer with prices in other countries, such as Germany (see above). After 3 months, the pricing commission advices the CRM about the acceptability or not of the proposed price level. But it is then the CRM that, based on the above-mentioned 4 criteria, may still decide that the price proposed by the manufacturer (and hence the proposed reimbursement level) is too high given the therapeutical need, the cost-effectiveness and the impact on the budget. The CRM will then force down the price and reimbursement level of the new drug.

Hence, the Belgian system does include, for already more than 10 years, a value-based pricing component.

The new principles and procedures, as set forth in AMNOG, will definitely have an impact on Belgian decisions as well, and it will be in 2 ways. First, the price commission will possibly observe lower prices than before in Germany which may lead to other decisions on approved Belgian prices. Second, and more importantly, the CRM will look carefully at the decisions in Germany related to added benefit of new drugs, and this will certainly influence the commission members. The issue of the right selection of comparator has not been sorted yet in Belgium, since, in contrast to, for instance, Australia, Canada, Sweden, and the UK, the practice of mixed treatment comparisons via network meta-analyses has not yet been well-adopted in Belgium.

CONCLUSIONS

The Act to Reorganise the Pharmaceutical Market (AMNOG) in Germany has obviously had a significant impact on the market access and pricing of new pharmaceuticals in Germany. The potential impact of AMNOG outcomes, especially GBA decisions, on the additional clinical benefit and the price decisions with the Spitzenverband der Krankenkassen, might have an impact in some other countries as well, as described in this article. Furthermore, the impact on future clinical development programs of new compounds may be significant as well. Further research and experience in Germany and other countries are needed and awaited. ■