Orphan drugs' market access challenges in Europe from a German perspective

Kirchmann T[1], Ewald A[2], Schönermark MP[1]
[1]SKC Beratungsgesellschaft mbH, Hannover, Germany, [2]Medizinische Hochschule Hannover, Hannover, Germany

Introduction and Objectives

Nowadays, market access of pharmaceuticals requires an health technology assessment (HTA) in most European countries. Particularly orphan drugs (ODs) are assigned a special role in most countries. The German AMNOG process belongs to the most straightforward and transparent HTAs in Europe. These procedure with subsequent price negotiations involving drugs with orphan drug designation (ODD) were evaluated and compared with results at European level to figure out success and failure strategies in Europe, especially in Germany. Challenges for the European market access of ODs were analyzed, mainly based on learnings from AMNOG procedures supported by results from the rest of Europe, especially HAS and NICE, also reflecting the inclusion of International Reference Pricing (IRP) in the price-determination mechanisms in the different countries.

Methods

- To identify strategies of success and failure, published documents of the early benefit assessments with orphan drugs in Germany were analyzed considering the results of their price negotiations. German decisions were compared to individual HTA decisions made at the European level (France, UK) in terms of time and content.
- Four drugs in four different therapeutic areas were investigated: asfotase alfa (metabolic disorder), tasimelteon (neurology), blinatumomab (oncology) and teduglutide (gastroenterology).
- In addition, External Reference Pricing (ERP) was considered especially from a German point of view since this could pose a major impact factor on the price determination process.

Results

	Asfotase alfa (Strensiq®) Metabolic disorder	**Tasimelteon (Hetlioz®)** Neurology	**Blinatumomab (Blincyto®)** Oncology	**Teduglutid (Revestive®)** Gastroenterology
Label Date of Approval	"Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease." **28 August 2015**	„Hetlioz is a medicine used to treat totally blind adults with non-24-hour sleep-wake disorder." **3 July 2015**	"BLINCYTO is indicated as monotherapy for the treatment of adults with Ph-/ CD19+ r/r BCP-ALL and paediatric patients after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation." conditional: **23 November 2015**; full: **18 June 2018**	"Revestive is a medicine for treating short bowel syndrome (or short gut) in adults and children aged 1 year and above." **30 August 2012**
G-BA[1]	• Non-quantifiable benefit based on mortality and ventilation-free survival outcomes in perinatal- and infantile HPP • High uncertainty with regard to effectiveness for juvenile HPP **Market availability since Oct 2015**	• Exclusive consideration of sleep times in the form of night and day sleep duration does not permit any direct conclusion with regard to the extent of the additional benefit (non-quantifiable benefit). **Market availability since Aug 2016**	• Non-quantifiable benefit based on missing control and lack of validity of the historical comparison ('16) • Considerable benefit based on not yet achieved significant improvement of the therapy-relevant benefit (moderate extension of OS w/o AEs) ('17) **Market availability since December 2015**	• Minor / non-quantifiable benefit based on not yet achieved moderate and not only marginal improvement of the therapy-relevant benefit. **Market availability since Sep 2014**
NICE[2]	• Previously only recommended for use in perinatal- and infantile-onset forms and guidelines did not endorse treatment for juvenile-onset form • Drug did initially not represent value for money. • Improved deal includes managed access agreement **Dec 2015 (perinatal/infantile), Jul 2017 (pediatrics)**	Not yet assessed! **No market availability**	• Recommendation due to an OS benefit of 3.7 months • Under substantial uncertainty, the ICER (£49,190) is within the acceptable threshold range considered a cost-effective use of NHS resources. **Market availability since Jun 2017**	• Teduglutide reduces, but does not remove, the need for intravenous nutrition and, therefore, it is not recommended. • Highly unlikely to lower ICER (£193,549) several fold to fall within the acceptable threshold range. **No market availability**
HAS[3]	• Favorable evolution of respiratory function in perinatal/infantile forms of the disease • Weaker evidence in juvenile forms of the disease • ASMR II (important improvement) **Market availability since Mar 2016**	Not yet assessed! **No market availability**	• Important therapy option in the field of application • No advantage over standard chemotherapy after allo-HSC; OS advantage not maintained over time • Feb 2016: ASMR III (moderate improvement) • Oct 2017: ASMR IV (minor improvement) **Market availability since Feb 2016**	• Effectiveness in reducing parenteral nutrition needs • Despite a modest level of evidence and in the absence of therapeutic alternatives and data on long-term efficacy and tolerance • ASMR III (moderate improvement) **Market availability since Dec 2014**

Comparison of HTA results in Germany, UK and France

The different outcomes of the HTA by G-BA (Germany), NICE (England) and HAS (France) show a varying but strong similarity between G-BA and HAS. Only Germany and France differentiate the clinical benefit of the drug by several categories. Analyzed assessments by the NICE, by contrast, provide almost consistently different from other HTA results with the exception of blinatumomab in the field of oncological diseases.

All three authorities agreed on the importance of blinatumomab as a new therapeutic option for the treatment of ALL, whereby G-BA and HAS already made this decision on the basis of the conditional approval, while NICE only made its recommendation with the full approval based on OS data.

The differences in decision making and NICE's focus on cost effectiveness and the price/cost ratio (value for money) of treatments become increasingly apparent when looking at the other procedures. While tedugludit is still not recommended due to its ICER of £193,549, also asfotase alfa, an enzyme replacement therapy for a highly lethal disease, is only recommended since July 2017 for the entire label population despite an ICER of £367,000, but with a managed access agreement. A comparison of HAS and G-BA in the assessments of both drugs shows that HAS primarily considers the severity of the disease, while G-BA focuses more on robust evidence and efficacy (see Table 1).

Germany	France	England
Robust evidence	**Disease severity**	**Cost effectiveness**
Efficacy	Health benefit	Price/cost of treatment
Health benefit	Unmet medical need	Health benefit
Benefit-to-harm ratio	Safety	Unmet medical need
HrQoL	Efficacy	

Table 1: Decision-making criteria in HTAs in Germany, France and England

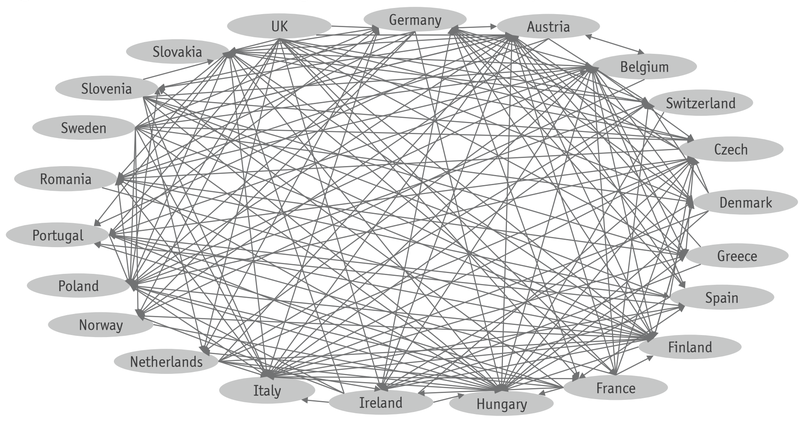
It is noticeable that in terms of market availability of the products Germany is the fastest, followed by France. In particular, the example of tasimelteon demonstrates the fast access for patients to innovative medicines in Germany. This is also supported by the fact that drugs in Germany can be prescribed to patients from the first day of their market launch and the early benefit assessment (the German HTA) starts in parallel. In contrast, the availability for patients of new drugs on the market in France and England only follows the HTA, apart from ATU (France) and PAS (England).

Impact of price-determination mechanisms in Europe

The mechanisms for determining the ultimate reimbursed price of a drug in the different countries are manifold.

In case of England, NICE committees consider only cost effectiveness thresholds on which basis their recommendations are made. If a recommendation has been made, the NHS is obliged to reimburse the costs. Therefore, it is up to the manufacturers to set the price to hit the threshold. Cost-effectiveness models can help to anticipate such thresholds.

Figure 1: Overview of country baskets and interdependencies in Europe[4]



But, UK prices are often used for setting reimbursement prices in other countries via external reference pricing (ERP). ERP is a cost containment tool systematically used by authorities in most of EU countries to set drug prices. In some countries, as Belgium, Finland, Italy, Poland, Spain, and Germany, ERP is used as a supportive method. Using ERP can lead to several interdependencies and downward spiral of drug prices over time (see Figure 1).

In France, the price of innovative medicines with ASMR of I to III is negotiated. Besides taking into account the price of the drugs with the same therapeutic indication, the projected or observed sales' volumes, the predictable or real conditions for use and the size of the target population, prices of these drugs should not set below the lowest price among one of France's reference countries, Germany, Spain, Italy, and the UK.

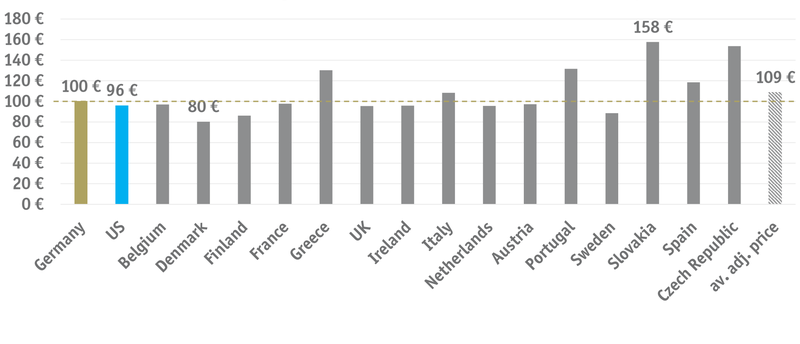
Figure 2: Impact of Germany's price on other countries prices as reference

→ Impact of the reference prices

In Germany, the price of a drug is negotiated with the umbrella organization of the SHIs (GKV-SV) on the basis of the additional benefit category granted by the G-BA before. Only in case of an additional benefit, two further elements are resorted to: the EU prices from a basket of 15 different countries and the prices of other comparable medicines. To have a single EU price for the negotiations, an algorithm is applied[5]. The prices of the European countries are first adjusted with their purchasing power parity (PPP) and then weighted with the sales in the respective countries. This often destroys a previously unified European price band. Figure 3 shows the impact of the PPP adjustment on EU prices, previously indexed to 100 Euro.

But not only the prices in other countries influence the German price, also the German price influences considerably the prices in other countries as Figure 2 shows. Besides 17 European countries, there are several countries from outside Europe, such as Canada, Japan and South Korea, which also resort to ERP with Germany in their country basket.

Figure 3: Impact of PPP adjustment on EU prices in Germany[5]



Conclusion

- Analyses show that Germany is the only country with no negative assessment for one of the drugs analyzed which is due to the legislation stating that the additional benefit for orphan drugs is granted by law. In contrast to England and France, however, in Germany the efficacy and robust evidence are of highest importance for the assessment. France does not have a negative rating either, but in terms of time to market availability it is somewhat behind Germany. In England pharmacoeconomic criteria, such as cost-effectiveness and cost-utility have a greater weight in the assessments, which is associated with a significantly lower number of positive recommendations and, therefore, reduced market availability of innovative medicines.
- ERP is defined as the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purpose of setting or negotiating the price of the product. Almost all EU countries apply ERP but Sweden and UK. A price drop in one country can lead to a downward price spiral due to the interdependencies between the countries as shown in Figure 1.
- In particular, the German example for calculating an EU reference price shows the importance of an early consideration of the underlying algorithm in the respective countries. Both interdependencies and the algorithms should be taken into account to finally derive the European launch strategy. In particular, Germany's impact on other countries as a reference should not be underestimated. Besides 17 European countries, there are several countries from outside Europe, such as Canada, Japan and South Korea, which also resort to ERP with Germany in their country basket. And even the US are planning to introduce international references, inter alia Germany.

References: 1 G-BA, Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V | 2: NICE, Technology appraisal guidances | 3: Haute Autorité de santé, Avis de la Commission de la Transparence | 4 Rémuzat C et al., „Overview of external reference pricing systems in Europe", Journal of Market Access & Health Policy, 2015 | 5 Rahmenvereinbarung nach § 130b Abs. 9 SGB V zwischen GKV-Spitzenverband und Verbände der pharmazeutischen Unternehmer, 2016

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SKC Beratungsgesellschaft mbH, Hannover, Germany | www.skc-consulting.de
Email: kirchmann@skc-beratung.de | Fon: +49 511 64 68 14-0
PHP325 – Poster presented at ISPOR Europe 2018, 10-14 November 2018 in Barcelona, Spain