# Quo vadis benefit assessment for orphan drugs in Germany. The end of the exception?

HTA34

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## INTRODUCTION

- Regulation (EC) 141/2000 on orphan medicinal products (OMPs) has two objectives:
  - Establishment of a community procedure for the designation of drugs as OMPs.
  - To create incentives for pharmaceutical companies to increase their research and development activities and the marketing of OMPs.[1]
- The regulation led to an increase in the number of OMPs available in Germany until today (previously: 5 OMPs; today 134 OMPs; as of February 2022).[2] With the therapies available to date, approximately 2% of rare diseases can be treated.[3] There is still a high medical need for new effective drugs in this field (”medical need"). This gap in care has reached attention on European level.
- In 2011, the International Rare Diseases Research Consortium (IRDiRC) has been found in response. The consortium has formulated several global goals for the decade 2017 – 2027. This includes that patients who are seeking for medical treatment for a suspected rare disease will be diagnosed within one year. (Currently, it takes an average of seven years to give a correct diagnosis[4]). Another goal: by 2027, 1,000 new therapies for rare diseases should have been approved, the majority of them for indications without alternative therapies.[5]
- In addition to the incentives on European level, Germany is the only European country having installed a special path for OMPs. Section 35a of the Social Code (SGB) V states that “[for] medicinal products that are approved for the treatment of a rare disease […] the additional medical benefit is **considered to be proven by the approval**; Evidence […] does not have to […] be submitted.” **Exception:** If sales exceed **50 million** euros within 12 months, a new regular benefit assessment is performed.
- The question whether the special regulation should be retained or abolished in the upcoming AMNOG reform is discussed controversially among the stakeholders (payers, HTA authorities, pharmaceutical industry).
- Payer side (SHI) and HTA authorities call for abolition of the special rule arguing that the additional benefit is fictitious and not justified.[6] Pharmaceutical companies state that the additional benefit has already been confirmed on European level by the Committee for Orphan Medicinal Products (COMP) and is therefore valid.[7]
- The goal is the approval of **1,000 new therapies by 2027.** To achieve this goal, are strategy how to deal with the annual costs for high-priced single therapies needs to be defined. To provide a fundamental **pricing and reimbursement strategy,** it is essential **to bring the comparative period and the costs into alignment**.

## OBJECTIVE

The primary objective of this analysis is to survey the status quo of the benefit assessment of orphan drugs in Germany, define if adjustments are necessary for the upcoming AMNOG reform and compare the German Market Access processes with France and England to determine whether certain processes could be adapted for Germany.

## METHODS

- Market Access processes for **Zolgensma®** (Onasemnogene Abeparvovec) were analyzed and compared to the three countries: **Germany, France and England.**
  - **France & England** were chosen as comparable countries because these three countries represent the largest pharmaceutical markets in Europe and have the most prominent HTA-based market regulations in the world.[8]
  - **Zolgensma®** was chosen because it is a high-priced single-use gene therapy, has generated much discussion between the stakeholders, and was the first OMP in Germany to be mandated by the Federal Joint Committee (G-BA) to **collect data accompanying its use.**[9] To do so, national health technology/reimbursement agency websites were assessed.
- **Expert interviews** were conducted with various stakeholders (pharmaceutical industry, payers, HTA agencies) from the three countries to gain a deeper understanding of the different processes and to be able to derive recommendations for the upcoming AMNOG reform regarding OMPs.

## RESULTS

### ANALYSIS MARKET ACCESS ZOLGENSMA® GER, FR, ENG

EU conditional marketing authorisation of Zolgensma®: **May 18, 2020**

**Table 1: Overview HTA Process Zolgensma® Germany**

| | Germany |
|---|---|
| HTA Agency | G-BA (Joint Federal Committee) & IQWiG (Institute for Quality and Efficiency in Health Care) |
| Process & Outcome Benefit Assessment | Suspension of the facilitated benefit assessment procedure because the €50 million sales threshold was exceeded in less than six months. Renewed regular assessment by IQWiG. Result: no additional benefit, requirement: data collection accompanying application |
| Time market availability | February 03, 2020 compassionate use; July 01, 2020 regular available & refundable |
| Patient population | all patients according to EMA approval |
| Therapeutic alternatives | Spinraza® (Nusinersen) (for the second assessment) |
| Reimbursement by SHI | fully prescribable & reimbursable |
| Costs for SHI | EUR 2.314.550,00 as of July 2020 |

## RESULTS

**Table 2: Overview HTA Process Zolgensma® France**

| | France |
|---|---|
| HTA Agency | HAS (High Authority of Health)<br>TC (Transparency Committee) |
| Process & Outcome Benefit Assessment | Two assessments. No special regulation for OMPs. Results: SMR (medical benefit) = important and ASMR (added medical benefit) = III (moderate), re-assessment planned in September 2022 (due to uncertainties related to serious risks of thrombotic microangiopathy (TMA)). |
| Time market availability | May 25, 2020 Cohort-ATU (temporary authorization to use) |
| Patient population | Available for limited patient population |
| Therapeutic alternatives | First evaluation: Spinraza® (Nusinersen); Second evaluation: additionally EVRYSDI® (Risdiplam) |
| Reimbursement by SHI | Reimbursement rate by SHI: 65%; reimbursement for part (50-60%) of label |
| Costs for SHI | Price not visible |

**Table 3: Overview HTA Process Zolgensma® England**

| | England |
|---|---|
| HTA Agency | NICE (National Institute for Health and Care Excellence) |
| Process & Outcome Benefit Assessment | HST (Highly Specialised Technology) procedure; NICE recommendation to NHS for part of patient population |
| Time market availability | March 08, 2021 via Managed Access Agreement (MAA) for part of the patient population |
| Patient population | Restricted patient population (incl. conditions) |
| Therapeutic alternatives | Best supportive care (BSC) |
| Reimbursement by NHS | Reimbursement by NHS for part of patients |
| Costs for NHS | Price: £1,795,000 as of July 07, 2021, less discount of unknown amount |

**Interim Conclusion:** The analysis shows that the benefit assessment in Germany is considered as a price mechanism rather than a supply mechanism. The differences in the assessments mainly impact the patient population and the timing of availability. From the patient's point of view, two decisive parameters.

### KEY FINDINGS EXPERT INTERVIEWS

- In Germany, there is a deficit in the SHI system, therefore, adjustments are inevitable.
  - Extreme position: abolition of OMP special pathway.
  - Compromise solution: special path only for therapeutic soloists.
  - Lowering of the turnover threshold from 50 to 20 million €.
- Unlike in England or France, there is **no fourth hurdle*** in Germany, which means that as soon as the product is approved, it is eligible for reimbursement once it hits the market.
- All interviews have been focusing on **price & pricing models** for OMPs. According to the experts, simple pricing models such as **discounts** can be implemented with the most impact.
- All three countries **prioritize OMPs**.
  - Germany has the **special pathway** for OMPs;
  - France is pioneer in establishing **centers of excellence** for diagnosis & treatment of rare diseases;
  - England has installed the **IMF** (Innovative Medicines Fund - limited to £ 340 million) and the **ILAP** (Innovative Licensing and Access Pathway - innovation passport for innovative medicines to reach indications with high medical need faster and better).

*The fourth hurdle is the assessment of the cost-benefit ratio immediately after approval. The obligation of the SHI to provide benefits depends on the result of this pharmacoeconomic evaluation. The first three hurdles include: safety, efficacy and quality.[10]

## DISCUSSION

- How should **high-priced single therapies**, for which the concept of annual therapy costs cannot be applied, be dealt with?
- Maintain orphan drug designation for **therapeutic soloists**.
  - Incentive for the company to conduct more research in areas which are still lacking therapeutic options ("real unmet needs").
- It is questionable whether **97 SHI** funds are necessary. Comparisons with France and England have shown that **fewer SHI** funds and a central health fund are **easier to manage**, especially with regard to pricing models. The more parties involved, the more difficult it is to implement.

## CONCLUSIONS

- German healthcare system enjoys a good international reputation.
- Abolition of the special rule for OMPs in Germany would probably not change the fast access for patients. Pharmaceutical companies have an eye on the global market and earn their money worldwide. Germany is too small and too insignificant for the abolition to have an impact.
- Germany ranks **first in Europe** in terms of **time to availability** and **rate of availability**[11].
- Focus should be on **"truly" rare diseases** (for which no therapy is yet available).
  - This could be addressed by **maintaining special rule for therapeutic soloists**.
- **HTA systems** in the three countries are **too different** for individual processes to be transferred to Germany.

[1]European Parliament. (2009). Regulation (EC) Nr. 141/2000 of EUROPEAN PARLIAMENT AND OF THE COUNCIL of December 16, 1999 on orphan medicinal products. [Online]. Available at: https://eur-lex.europa.eu/EN/legal-content/summary/medicines-for-rare-diseases-orphan-drugs.html [Accessed March 2022] [2]vfa. (2022). Zugelassene Orphan Drugs. [Online]. Available at: https://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/orphan-drugs-list [Accessed March 2022] [3]vfa bio. (2021). Vfa-/vfa bio-Positionspapier Orphan Drugs ZUSAMMENFASSUNG. [Online]. Available at: https://www.vfa-bio.de/vb-de/vb-presse/vb-positionen [Accessed April 2022] [4]ATSE. (n.d.). Die Erforschung & Entwicklung von Orphan Drugs: Ein Geschäftsmodell und seine Besonderheiten. [Online]. Available at: http://media.celgene.com/content/uploads/sites/6/RPP-E-009-16-ATSE-Positionspapier.pdf [Accessed March 2022] [5]IRDiRC. (2022). Vision & Goals. [Online]. Available at: https://irdirc.org/about-us/vision-goals/ [Accessed April 2022] [6]IQWiG. (2022). Orphan Drugs: Privileg des „fiktiven“ Zusatznutzens nicht gerechtfertigt. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) [Online]. Available at: https://www.iqwig.de/presse/pressemitteilungen/pressemitteilungen-detailseite_58496.html [Accessed March 2022] [7]vfa bio. (2021). *Vfa-/vfa bio-Positionspapier Orphan Drugs ZUSAMMENFASSUNG*. [Online]. Available at: https://www.vfa-bio.de/vb-de/vb-presse/vb-positionen [Accessed April 2022] [8]Häussler, B. (2019). HTA-Verfahren zur Bewertung von Arzneimitteln: Unterschiede in Europa und Trends. *PM QM Fachzeitschrift für pharmazeutische Medizin und Qualitätsmanagement*, (1). [Online]. Available at: https://www.iges.com/sites/igesgroup/iges.de/myzms/content/e6/e1621/e10211/e23547/e23909/e23910/e23916/attr_objs23925/Haeussler_HTA_in_Europa_PMQM_1_2019_ger.pdf p.26ff [9]Storm, A. (2022). AMNOG-Report 2022 Orphan Drugs—Erstattungs- und Versorgungsherausforderungen (Bd. 38). Heidelberg: medhochzwei Verlag GmbH. P. 37 [10]Ärzteblatt. (2003). „Vierte Hürde“ im Gesundheitswesen: Auf Kosten und Nutzen geprüft. Deutsches Ärzteblatt [Online]. Available at: https://www.aerzteblatt.de/archiv/35775/Vierte-Huerde-im-Gesundheitswesen-Auf-Kosten-und-Nutzen-geprueft [Accessed July 2022] [11]EFPIA Patients W.A.I.T. Indicator 2021 Survey [Online]. Available at: https://www.efpia.eu/media/676539/efpia-patient-wait-indicator_update-july-2022_final.pdf [Accessed September 2022]. **Please contact us for an overview of all sources used: liza2@gmx.de**