Enzyme replacement therapies within the German HTA (AMNOG) process

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Introduction

Enzyme replacement therapies (ERTs) are used to treat genetic metabolic diseases, which occur rarely and present extremely heterogeneous disease manifestations[1]. ERTs replace the missing enzyme exogenously and in turn, restore downstream molecular pathways. Although these targeted therapies represent a new treatment option compared to the hitherto available symptomatic, non-curative therapies, they are cost-intensive and a lifelong medication is essential. The rarity and heterogeneity of the diseases implies few and dispersed patients and experts in the field of application impeding the evaluation within the German HTA (AMNOG) process.

Methods

ERTs assessed by the Federal Joint Committee (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG) were examined in a systematic database search[2]. Subsequently, the relevant entries were analyzed in terms of indication, trials, treatment costs, added benefit and reimbursement rebate. Additionally, treatment costs were obtained from the database Lauer-Taxe[3]. The research considered all completed AMNOG assessment procedures from 2011 to June 2018.

Results

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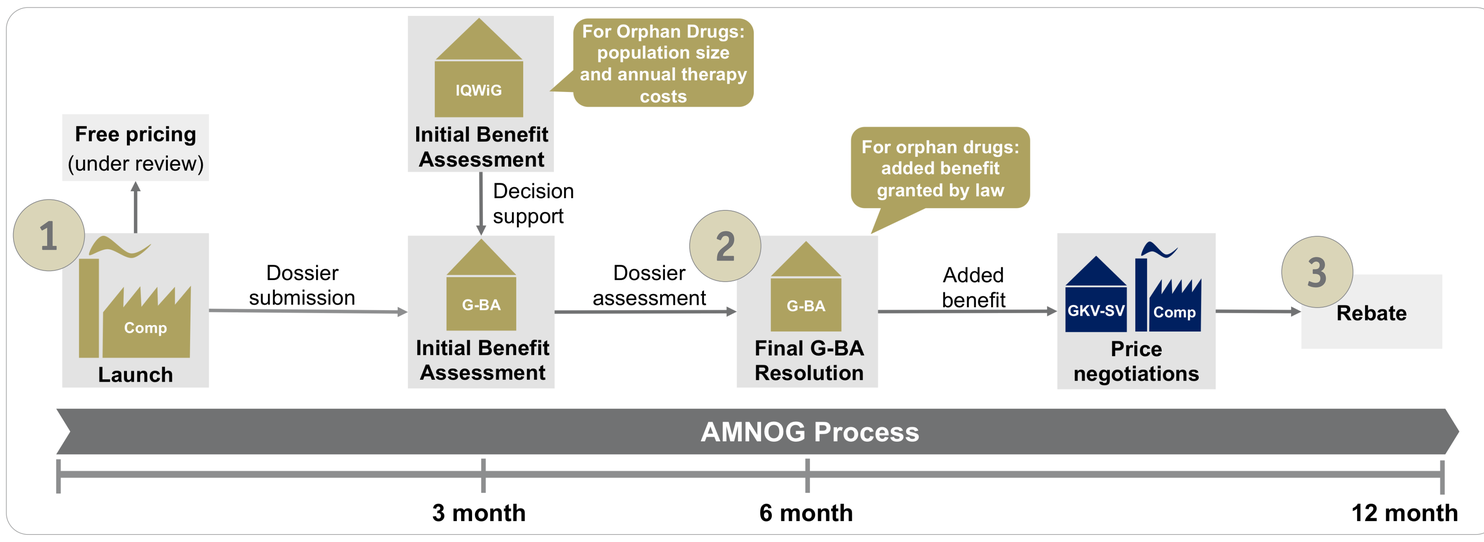
DRUG (TRADE NAME)	INDICATION	ORPHAN DRUG	LAUNCH PRIZE (annual costs per patient) [a, b]	LAUNCH GERMANY	POPULATION GERMANY [c]	PIVOTAL STUDY	STUDY DESIGN	STUDY PATIENT NUMBER
Asfotase alfa (Strensiq®)	Pediatric HPP (perinatal/infantile- and juvenile-onset HPP)	✓	1,973,308.22 €	Oct 1st, 2015	1000	ENB-006-09 ENB-008-10	Open-label study (extension study)	13 (12)
Cerliponase alfa (Brineura®)	NCL2	✓	607,210.76 €	Jun 1st, 2017	20 – 40	190-201 (190-202)	Open-label study (extension study)	24 (23)
Elosulfase alfa (Vimizim®)	Morquio A syndrome (MPS IVA)	✓	1,350,291.80 €	Jun 1st, 2014	20 – 100	MOR-004 (MOR-005)	RCT – Placebo (extension study)	177 (173)
Sebelipase alfa (Kanuma®)	LAL deficiency fast progredient < 6 month LAL deficiency not-fast progredient > 6 month	✓	439,491.52 € [d] 878,983,04 €	Oct 1st, 2015	4 - 5 27 - 838	LAL-CL03 LAL-CL02	Open-label study RCT – Placebo	9 66

HPP – hypophosphatasia; LAL - lysosomal acid lipase; MPS – mucopolysaccharidosis; NCL2 - neuronal ceroid lipofuscinosis 2; RCT – randomized controlled trial;
a: weight-based dosing (average adult with 76,3 kg acc. to microcensus Germany); b: ex-factory prize reduced by §130a SGB V (7%); c: GKV-patients acc. to G-BA; d: based on the average weight of 4,9 kg (LAL-CL03) included in the study



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DRUG	REBATE	ANNUAL THERAPY COSTS/ PATIENT [a]
Asfotase alfa	35%	1,277,952.00 €
Cerliponase alfa	13%	530,000.12 €
Elosulfase alfa	11%	1,200,940.00 €
Sebelipase alfa	30%	308,193.60 € 616,387.20 €

a: Current as of 11/07/2018

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DRUG	BENEFIT [a]- ASSESSMENT	ADDED BENEFIT	LIMITED RESOLUTION	REGISTRY [b]
Asfotase alfa	+ Benefit in overall survival and the (invasive) ventilation-free survival in patients younger than 5 years; improvement of growth and motor function in patients 5-12 years - Lack of prospective parallel control groups; high bias potential of indirect comparison due to natural history studies as well as the open-label single-arm trial design; low patient numbers; no significant improvement in patient-relevant endpoints for patients 13-66 years	Non-quantifiable	Yes (Dec 2019)	Yes
Cerliponase alfa	+ Significant maintenance of patient-relevant motoric and linguistic abilities (primary endpoint) - High bias potential due to the non-adjusted indirect comparison with natural history control (patient registry data) → no sufficient similarities in the patient characteristics; uncertainties in validity of primary endpoint; no comparative analyses for QoL and safety endpoints	Non-quantifiable	Yes (Jun 2021)	Yes
Elosulfase alfa	+ Relevant reduction of symptoms; significant advantages in primary endpoint (6MWT, accepted as clinically relevant primary effect by EMA) - Limited study duration; occurrence of adverse events; no long-term efficacy or safety data available	Minor	No	No
Sebelipase alfa	+ Overall benefit in the overall survival (fast progredient population) - High bias potential due to the open label, single arm trial design and comparison to a natural history study; lacking validation of surrogate parameters, main efficacy results in surrogate parameters; patient-relevant endpoints did not show relevant differences (not-fast progredient population); no long-term efficacy or safety data available	Non-quantifiable	Yes (Dec 2020)	Yes

a: main critical and positive points raised by the G-BA; b: requested by G-BA

Conclusion

For the treatment of orphan diseases, ERTs face different challenges during the market access process. Due to the small number of study patients and the heterogeneity of the diseases the evidence regarding the benefit is limited, resulting in time-restricted resolutions. To obtain more evidence, G-BA linked the resolution with a request to set up a disease-specific registry. For orphan drugs, the current regulations acc. to §35a SGB V grant at least a *non-quantifiable* benefit. The G-BA therefore only determines the extent of the additional benefit for the various patient groups. This extent is the central criterion for reimbursement negotiations, which also follow the benefit assessment for orphan drugs. The price negotiations may, however also be driven by other factors, e.g. the launch price, precedents and the severity of the disease. As the level of evidence is often sparse for orphan diseases, evidence collection in form of registries will be requested more often in the future. The individual market access strategy of specific products should therefore be aligned with German HTA requirements early in the process, including setting up a patient registry.

References: 1 Li M (2018), Pediatr Ann | 2 https://www.g-ba.de | 3 https://www.cgm.com/lauer-fischer/index.de.jsp

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