Focus: Paediatric marketing authorisations

Paediatric medicinal products and special features of paediatric studies in the AMNOG

The development and accessibility of paediatric medicinal products are subject to special support and regulation in the EU. As part of market access, new medicinal products undergo a benefit assessment in accordance with Section 35a SGB V after the German Act on the Reform of the Market for Medicinal Products (AMNOG) came into force in 2011. The additional benefit is assessed by the Federal Joint Committee (G-BA), after which the reimbursement amounts are negotiated with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). Drugs that are given a new area of application are also subject to benefit assessment. These include extensions of the indication for paediatric patients. Medicinal products with a so-called PUMA authorisation (Paediatric Use Marketing Authorisation) are also affected by the AMNOG. The practical experience to date with the AMNOG benefit assessment for medicinal products with such authorisations is described below. The focus here is particularly on taking into account the special features of conducting paediatric clinical trials.

>> Regulation (EC) No. 1901/2006, which has been in force since 2007, is of central importance for the development and authorisation of paediatric medicinal products. The purpose of the regulation is to promote the development and accessibility of medicinal products for use in the paediatric population. At the same time, it is intended to ensure that medicinal products are developed and authorised within the framework of ethical and high-quality research. Since 26.07.2008, a Paediatric Investigation Plan (PIP) with a development programme for use in children must also be submitted as a rule for newly authorised medicinal products. A PIP must be approved by the Paediatric Committee (PDCO) at the EMA and is part of the marketing authorisation documentation, whereby a deferral or exemption can be applied for (BfArM 2023). Another special form of marketing authorisation for medicinal products under this regulation is the Paediatric Use Marketing Authorisation (PUMA). Such an authorisation, which is limited exclusively to use in the paediatric population, can be granted for off-patent medicinal products that are already authorised for adults. This authorisation may also include the development of child-friendly pharmaceutical forms.

Integral recitals of Regulation (EC) No 1901/2006 also state that the above objectives should be achieved ‚without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of a medicinal product for other age groups.' In this respect, the work of the PDCO must consider ‚whether the trials have a potentially significant therapeutic benefit for the paediatric patients participating in them or for the paediatric population in general'. The principle of avoiding unnecessary clinical or other trials involving the paediatric population is of central importance here and is therefore also the subject of Article 1 of the Regulation. At the same time, it is noted that paediatric clinical trials may require specific expertise and methodology. Of particular relevance in the context of this analysis is the possibility of using paediatric extrapolations in the authorisation process. This refers to the process of generating and transferring evidence regarding efficacy and safety if it can be assumed that the course of the disease and the expected response to a medicinal product are sufficiently similar in the paediatric population and the reference population (adults or older children) (EMA 2017, EMA 2018). The use of models and simulation techniques to derive findings on pharmacokinetics and pharmacodynamics is equally relevant for this.

Framework of the AMNOG benefit assessment for paediatric medicinal products

As already mentioned in the introduction, medicinal products with a PUMA authorisation are covered by the AMNOG assessment. This is directly regulated in Chapter 5, Section 2 (1) VerfO. Accordingly, ‚medicinal products for which a marketing authorisation for paediatric use has been granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/2004 pursuant to Article 38(1) of Regulation (EC) No 1901/2006' are considered to be medicinal products with new active substances. New indications for paediatric patients that have been authorised via a PIP are also subject to the broad definition of new indications and therefore also to the AMNOG obligation (G-BA 2023) in accordance with Chapter 5, Section 2 (2) VerfO.

Since the SHI Drug Supply Strengthening Act (AMVSG) came into force on 13 May 2017, there has only been a legal requirement for the handling of paediatric medicinal products in accordance with Section 5 para. 5a AM-NutzenV (German Drug Benefit Assessment Ordinance). It regulates the requirement for the G-BA to review evidence transfer for PUMA medicinal products. Accordingly, ‚the Federal Joint Committee examines whether an additional benefit can be recognised for patient groups or sub-indications that are covered by the marketing authorisation but are not or not sufficiently represented in the study population and for which the marketing authorisation was granted on the basis of the transfer of evidence. In these cases, it can recognise an additional benefit if the transfer of evidence is permissible and justified in accordance with the current state of scientific knowledge, also with regard to the benefit assessment.' It also states that the G-BA regulates the details in its rules of procedure. However, a look at the G-BA's procedural regulations does not reveal any regulations that would reflect a procedure for the transfer of evidence.

The legal justification for the AMVSG emphasises that due to the special requirements for conducting clinical trials with children, it is possible that there is not sufficient

evidence to prove an added benefit for all authorised patient groups, particularly in the case of PUMA medicinal products. The requirement to review a transfer of evidence therefore takes into account the ‚special features of medicinal products with a marketing authorisation for paediatric use', according to the explanatory memorandum. At the same time, it is recognised that ‚studies in children are subject to special requirements and the number of study participants must be kept to a minimum' (BMG 2016). The limiting wording of the requirements and the explanatory memorandum suggests that this was clearly intended to address the special circumstances from the benefit assessment of the PUMA drug propranolol (Hemangiol®) from 2015. In this assessment, the G-BA extrapolated the results between different patient groups of a decision with different degrees of disease severity. The G-BA also followed the assessment of the regulatory authority on extrapolation, also taking into account the special features and limitations of conducting paediatric clinical trials with regard to the avoidance of unnecessary studies and the specific expertise and methodology that may be required (G-BA 2015).

Although the AM-NutzenV only stipulates that evidence transfer is to be examined for PUMA medicinal products, the G-BA still reserves the right to examine the possibility of evidence transfer for paediatric extensions of the therapeutic area. This became clear in the benefit assessment of the active substance vandetanib on 6 July 2017 (a few days after the AMVSG came into force) (G-BA 2017). The procedure with an indication extension for children aged 5 years and older in the treatment of thyroid carcinoma outlined the possible pattern for the procedure of an evidence transfer.

For the target population of adults, the G-BA previously saw an indication of minor added benefit. The EMA's findings regarding the identical cause of the disease, the comparability of the clinical picture and comparable pharmacokinetic parameters as well as comparable efficacy and safety based on the study data from the randomised controlled adult study and the single-arm children's study were used as the minimum requirement for a transfer of evidence based on this (G-BA 2017). A further decisive criterion was therefore the identical appropriate comparator therapy for children and adults defined by the G-BA. At the same time, when recognising the evidence on the basis of a lower (than RCT) evidence level, the G-BA also acknowledged the special features and limitations of conducting paediatric studies, including the very small number of patients. Weighing up further factors such as the lack of availability of alternative therapies, the severity and rarity of the disease, the G-BA saw an indication of a non-quantifiable added benefit in the context of an evidence transfer.

The AMNOG balance sheet for paediatric medicinal products

Given the legal and methodological requirements for the benefit assessment of paediatric medicinal products outlined above, the question now arises as to how such medicinal products fare in the AMNOG balance sheet and how the anchored possibility of evidence transfer is utilised. For this purpose, all completed procedures were recorded in the vfa's AMNOG procedure database. As of 24 November 2023, the database contained 82 completed procedures for paediatric indication extensions (PIP) and 6 procedures for PUMA approvals, which related to a total of 54 medicinal products. The most common therapeutic areas included endocrine, nutritional and metabolic diseases (32 procedures), infectious diseases (27), diseases of the nervous system (10) and oncological diseases and neoplasms (6). According to the G-BA, the SHI target population for PUMA procedures was between 980 and an estimated maximum of 86,000 patients.

For PIP indication extensions, the range was between 1 and 20,200 patients with a median of 125, meaning that a high proportion of these procedures only affected a small target population.

When interpreting these and the following figures, it should be noted that of the 88 procedures, 25 alonerelated to the treatment of cystic fibrosis in new PIP indications with theactive substance ivacaftor or combinations containing ivacaftor. Thirty of the 88 procedures concerned medicinal products for the treatment of rare diseases (orphan drugs). Looking back over the last few years, there has been a significant increase in AMNOG procedures for new paediatric indications in particular (Fig. 1).

The additional benefit balance is shown in Figure 2. The proportion of PIP procedures with an unproven added benefit of around 58% is particularly striking, as this is higher than the proportion for all other AMNOG procedures (around 47%). Also striking is the low proportion of a quantifiable extent (minor, considerable or substantial) in cases of proven added benefit of only around 6%. Taking into account the procedures without

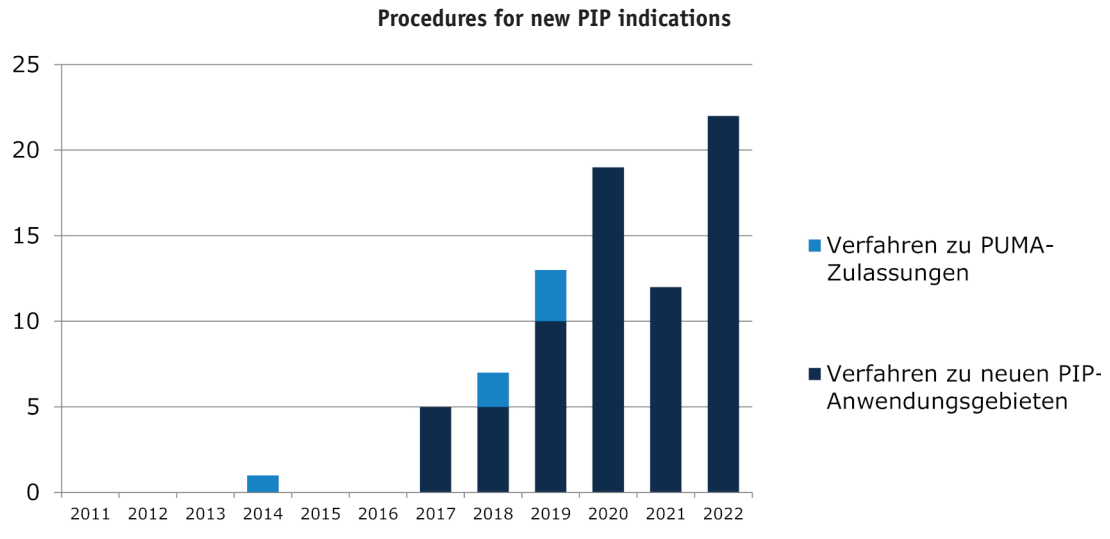


Fig. 1: Procedures for new PIP indications over time (after the start of the AMNOG procedure).

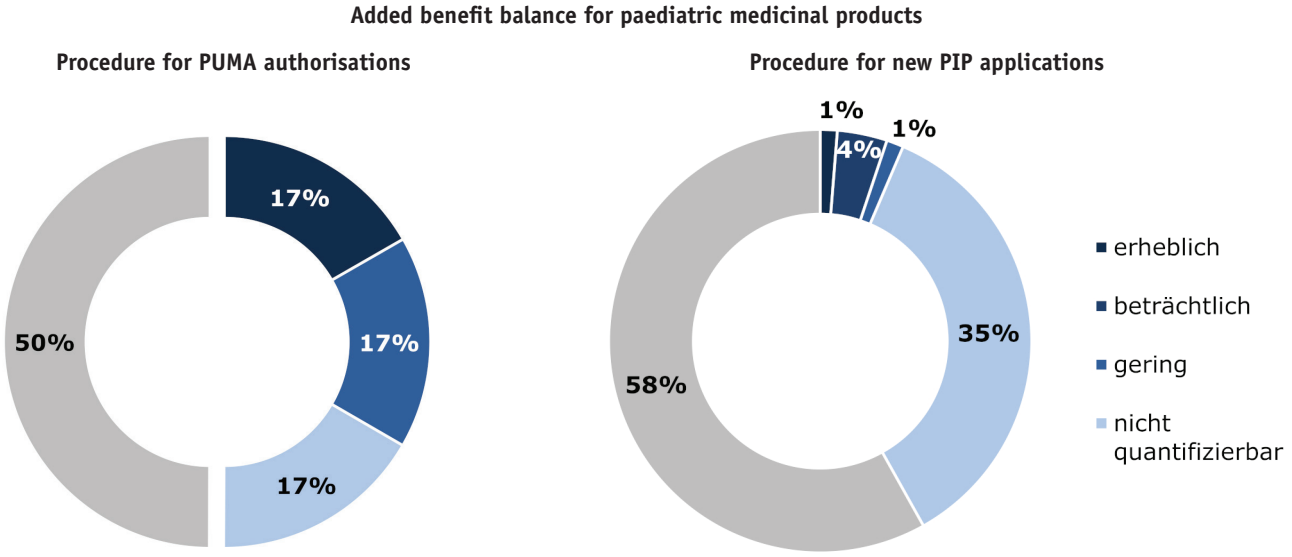


Fig. 2: Added benefit balance for paediatric medicinal products.

orphan drug status, the proportion of PIP procedures with an unproven added benefit is 74% and the proportion of a quantifiable added benefit is only 4%. For the PUMA authorisations, the significance of the added benefit measures is less meaningful in view of the small number of cases (N = 6).

In 6 procedures on 5 PUMA marketing authorisations (propranolol, glycopyrronium bromide, hydrocortisone, melatonin, 2 times vigabatrin), a dossier with an RCT was available in 3 procedures. A transfer of evidence was reviewed in 2 procedures (propranolol, hydrocortisone) and considered by the G-BA in one (propranolol).

In around 45% of the PIP indication extensions (36 of 82 procedures), an RCT justifying authorisation was available for the benefit assessment. In 37 procedures, the possibility of evidence transfer was discussed in the reasons for the decision and accepted by the G-BA in 18 of these. However, these findings require separate consideration for a meaningful interpretation in the following discussion.

Discussion of AMNOG assessment practice

Conditions for evidence transfer

After the positive use case in the vandetanib procedure, it became apparent in the further course of the procedure that the requirements for evidence transfer in the benefit assessment for PUMA drugs represent a high hurdle. This was evident, for example, in the subsequent procedure on hydrocortisone (Alkindi®), in which no evidence transfer was carried out because no controlled studies (including on adults) were available on individual formulations with hydrocortisone. This is despite the fact that the G-BA also acknowledged in its considerations that the development of a medicinal product for use in children must follow the paediatric investigation plan approved by the PDCO, which is intended to ensure that children are not exposed to avoidable clinical trials and that a direct comparative study was therefore not part of the authorisation (G-BA 2018a). At the same time, the added value of safe dosing for infants and children was not recognised as an additional benefit.

In the G-BA's decision-making practice, the EMA's findings on the medical rationale for the transferability of such data represent a sufficient rather than a necessary condition for the acceptance of evidence transfer. They can be decisive for PIP indication extensions (e.g. for cystic fibrosis), but are not in all cases (G-BA 2022, G-BA 2023). For example, although the G-BA may take note of the fact that the authorisation is based on an extrapolation of pharmacokinetic and pharmacodynamic data, this alone does not allow the additional benefit to be recognised (G-BA 2021c). However, a necessary condition for a transfer of evidence with a recognition of added benefit is a previously proven added benefit in the adult population. Another necessary criterion for a transfer of evidence is the requirement of an identical appropriate comparator therapy for adults and for subsequent paediatric extensions (G-BA 2021b). The deviations in the appropriate comparator therapy can result not only from differences in treatment standards and the availability of authorised therapies, but also from rapid changes in healthcare practice in the time between benefit assessments (G-BA 2018b). This is particularly explosive, as the AMNOG procedures for paediatric extensions of a therapeutic area onlystart on average around 5 years aftera medicinal product is first placed on the market. In addition, there are further hurdles with regard to the presentation of the comparability of disease progression or the usual requirements for the suitability of methodological analyses or the completeness of all patient-relevant outcomes.

Limitations of the results on evidence transfer

Past procedures have shown that evidence transfer was accepted by the G-BA in 18 procedures, but only in 3 therapeutic areas (cystic fibrosis, chronic hepatitis C and atopic dermatitis). However, it should be noted that these are only 11 procedures for the active substance ivacaftor or combinations containing ivacaftor, in which a transfer of evidence (partly in the presence of an RCT) was carried out in a comparable constellation for smaller extensions of the authorised age groups and genotypes. In 4 further cases, this concerns the treatment of chronic hepatitis C, which is an exception in the AMNOG, even in adults, due to dramatic

effects and the consideration of single-arm studies. In 2 further procedures on the active substance dupilumab for the treatment of atopic dermatitis, RCTs justifying approval were available for the assessment in the respective paediatric age group (G-BA 2021e, G-BA 2023). In principle, these RCTs could have led to an added benefit even without evidence transfer, but were only used by the G-BA as a supplement, in particular due to the standard requirement of at least 24 weeks for the duration of studies for chronic diseases in the AMNOG not being met. In one of the procedures, the transfer of evidence was also limited to a patient group in which the clinical picture was sufficiently similar to that of adults (G-BA 2023). Outside of these cases, evidence transfer on the basis of non-randomised evidence for children was thus only carried out in one procedure on vandetanib in 2017 (already described above) (G-BA 2017).

One limitation of the analysis is that no procedures were systematically included in which, due to the respective disease, only children and adolescents (e.g. juvenile psoriatic arthritis) or, in addition to adults, a paediatric subpopulation under the age of 18 (e.g. Hodgkin's lymphoma, melanoma) were included in the approval. Although the latter occur more frequently, they do not represent a paediatric indication extension in the narrower sense. At the same time, such procedures make it considerably more difficult to analyse the treatment of paediatric patients, as they are rarely identified by the G-BA as a separate issue in the decision (e.g. for approvals from the age of 12). In some cases, however, evidence transfer may also be important for such procedures (G-BA 2021a). A further limitation may result from the anticipated G-BA requirements for evidence and evidence transfer, as in some cases pharmaceutical companies do not even seek proof of added benefit for paediatric indications with reference to the formal requirements.

Further requirements for the added benefit

The special features and limitations in the conduct of paediatric clinical trials for the recognition of evidence below an RCT are only mentioned and taken into account in a few exceptional cases in the G-BA's supporting reasons (G-BA 2015, G-BA 2017, G-BA 2022). Nevertheless, the AMNOG also applies the basic requirement to submit studies of the highest evidence level (RCT) for paediatric marketing authorisations. To derive evidence of added benefit as the highest possible level of certainty, two RCTs are generally even required (as for adults). This requirement should be questioned, especially for paediatric populations.

In addition to the high proportion of unproven added benefit, the very low proportion of quantifiable added benefit for new paediatric indications was also conspicuous in the analysis. In the case of quantifiable added benefit, RCTs justifying authorisation were (expectedly) available in all 6 procedures. For all other PIP indication extensions with an added benefit, this was categorised as non-quantifiable by the G-BA. The reason for the non-quantifiable extent was the transfer of evidence (with and without supportive RCTs), the existing uncertainties of an RCT (e.g. due to low patient numbers) or the orphan drug status of a medicinal product with non-randomised approval data (G-BA 2019, G-BA 2021d). In this context, the ‚guard rails' anchored in the SHI Financial Stabilisation Act (GKV-FinStG) since the end of 2022 with their effects on the negotiations of the reimbursement amount must also be considered. The proportion of procedures with at least a considerable additional benefit was only 5%. This raises the question of whether not only the requirements for the added benefit itself, but also for quantifiability, do justice to the special features of studies in paediatric settings.

A further requirement for the proof of added benefit is, as is well known, the existence of therapeutic benefits in so-called patient-relevant outcomes. In this respect, it is not apparent that the particularities of conducting paediatric studies are systematically taken into account in the AMNOG procedures. The only exception to the rule is the consideration of the endpoints ‚lung clearance index' and ‚body mass index' in cystic fibrosis (G-BA 2022).

Availability of paediatric medicinal products

With regard to availability, it should be noted that of the PUMA medicinal products analysed, vigabatrin (Kigabeq®) was no longer available at the time of the analysis. The medicinal products with a PIP indication extension included in the present analysis were available in Germany. However, it should be borne in mind that the AMNOG procedures for paediatric extensions of an indication start several years after the new medicinal products are first placed on the market. The products concerned were therefore generally available in Germany with a reimbursement amount at this time. At the same time, the absolute size of the new paediatric target populations and their share of the total SHI target population of a medicinal product relevant to the negotiations were small in many cases. Thanks to this initial situation, a predominantly unproven additional benefit for paediatric indications has not yet led to further market withdrawals in the subsequent negotiation framework. However, it must be questioned whether this should be a yardstick for assessing the framework conditions. Rather, the results indicate that the paediatric indication extensions remain available in healthcare despite the rigid framework of the AMNOG benefit assessment. The actual anchored promotion of the development and availability of paediatric medicinal products is rather counteracted by this.

Outlook

It should be noted that the problem of the benefit assessment of paediatric indication extensions has now become a normal case that is hardly noticed. In the recent past, the relevance of paediatric medicinal products has generally come more into focus in German pharmaceutical policy. Following the acute supply problems caused by supply bottlenecks, measures were taken to improve the supply of generic paediatric medicines with the German Act to Combat Supply Bottlenecks and Improve Supply (ALBVVG). However, the development, availability and evaluation challenges of patent-protected paediatric medicines have not yet played a prominent role in the discussions surrounding the AMNOG.

Appropriateness of the assessments

In its primary function as an instrument of price regulation, the AMNOG should contribute to the reduction of pharmaceutical expenditure. This now results in annual savings of several billion euros for the statutory health insurance funds. However, at least

in the case of paediatric indication extensions with a very small target population, the question arises as to whether the implementation of an extensive AMNOG procedure does not cause more costs for the insured community than the potentially achievable savings. The appropriateness of many such benefit assessments for the objective of achieving savings in SHI appears debatable from a health economic perspective.

Requirements for evidence transfer

The instrument of evidence transfer has only been used by the G-BA in a few special cases in just three therapeutic areas in recent years. The intention of the legislator in stipulating evidence transfer in accordance with Section 5 (5a) of the German Paediatric Benefit Regulation (AM-NutzenV) was to take better account of the special features of paediatric medicinal products. However, the regulation primarily covers the special case of evidence transfer between patient groups or sub-indications. For the transfer of evidence from an adult population to a PIP indication extension, the decision practice of the G-BA applies. The prerequisite of a previously proven additional benefit for the older target group of the older population appears comprehensible at first glance. Nevertheless, for the target population of children, the relevance of care, the added benefit and also the underlying endpoints can have an independent significance. The prerequisite of an identical appropriate comparator therapy must also be scrutinised. Both known differences in the availability of authorised treatment options in children and the fact that such procedures are several years away from being placed on the market for the first time are likely to lead to more frequent deviations. Overall, the rather rigid requirements for the possibility of evidence transfer should be reviewed.

Consideration of the special features of therapeutic situations

It is of central importance for the promotion of the development and availability of paediatric medicinal products that the particularities and limitations of conducting paediatric clinical trials are taken into account as part of the approval process. These particularities have now also been recognised in the AMNOG benefit assessment when

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applying evidence transfer. In more recent assessment practice, such references are rarely found in the supporting reasons for the G-BA's decisions. Although the central objectives of the authorisation and an HTA-oriented added benefit assessment vary, it is nevertheless necessary to question whether the special features of conducting paediatric studies should be systematically taken into account as an assessment criterion within the framework of the AMNOG. This also applies in the context of the other general requirements in the AM-NutzenV. Accordingly, there are cases in which it is ‚impossible or inappropriate to conduct or require studies of the highest evidence level'. In these special therapeutic situations, ‚evidence of the best available evidence level must be submitted'. This requirement has no consequences in practice, as the possibility and appropriateness of clinical trials at the highest level of evidence are not systematically reviewed and non-randomised trials are generally considered unusable (vfa 2023). In the AMNOG, this applies not only to paediatric medicinal products, but also to adults. For paediatric marketing authorisations in particular, however, the question arises as to whether the available evidence does not already regularly take into account the special features of conducting paediatric clinical trials (also with regard to avoiding unnecessary trials) or whether the highest possible level of evidence already exists. In such special cases, the requirements for study design and certainty of results should also be subject to critical discussion. <<

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Citation

Rasch, A.: ‚Paediatric drugs and special features of paediatric studies in the AMNOG', in „Monitor Versorgungsforschung" (01/24), S. 38–43. http://doi.org/10.24945/MVF.01.24.1866-0533.2577