AIM Fair Price Calculator for Patent-Protected Medicines

An approach to calculating fairer pharmaceutical prices in the EU and beyond

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Summary

Patent-protected drugs are one of the main cost drivers for statutory health insurance (GKV). Despite a relatively low prescription frequency, they account for almost half of all pharmaceutical costs due to their very high prices. For this reason, the International Association of Mutual Benefit Societies (AIM) has developed a model for calculating fair and transparent prices for medicines, based on objective criteria. These are based on the manufacturers' costs as well as the usual market margins. This study shows how the prices of a selection of high-cost drugs, determined by using the AIM *Fair Pricing Calculator*, compare with the current annual costs of treatment. The prices charged are two to 13 times higher than they should be from a fair pricing point of view. Weighted by sales, this results in a cost overrun of about 173% for patent-protected drugs. Extrapolated to total health insurance expenditure, the AIM model therefore shows a savings potential of around 13 billion euros per year, with an upward trend. The *fair pricing calculator* is an enrichment in the discussion on fair prices of medicines and should be seen as additional information for price negotiations, as well as an incentive for manufacturers to create transparency on research and production costs.

The problem of high drug prices

In Germany, statutory health insurance (GKV) is one of the pillars of social security. The monthly contributions paid are redistributed in solidarity in the event of illness, i.e. in the event of a claim for benefits

- from healthy contributors to sick contributors,
- from the young to the old (the burden of disease is generally higher in later life),
- from single persons to families with children (non-contributory family insurance) and
- from high-income contributors to the low-income threshold (percentage contributions based on salary with the same overall benefits for all persons receiving compulsory health insurance) (BMG, 2021).

According to KJ1 statistics, total health insurance expenditure in 2020 amounted to 248.88 billion euros, which is an increase of 3.9% compared to the previous year with expenditure of 239.49 billion euros (GKV-SV, 2021st). After expenditure on hospital treatment with €81.55 billion (32.8%) and medical treatment with €43.99 billion (17.7%), GKV expenditure on pharmaceuticals comes in third place with €43.29 billion (17.4%) (GKV-SV, 2021a; GKV-SV, 2021b; GKV-SV, 2021c).

A *detailed* analysis of health insurance expenditure on medicines as published annually in the Pharmaceutical Prescription Report reveals that patent-protected medicines account for a large proportion of insurance expenditure on medicines. While the turnover of these original preparations was 7.5 billion euros in 2000 (38.8% share of the total market), it is expected to reach 21.6 billion euros (46.3%) in 2019, almost tripling. The asymmetry between sales volume and turnover of patent-protected drugs by *defined daily dose* (DDD) is particularly striking. In 2019, consumption was 2.8 billion DDD (6.4%) for those with patent protection, compared with 38.2 billion DDD (87%) of generic drugs, for a total of 43.9 billion DDD (Schwabe&Ludwig, 2020).

The pricing of patent-protected medicines therefore requires special attention. Since 2011, when the German Drug Market Reorganisation Act (AMNOG) was introduced, pharmaceutical companies have been free to set the market entry price of their new drugs for one year. Companies are thus faced with a price-insensitive GKV demand and are at the same time protected from competition, which prevents a price setting based on market signals. The price thus loses any relation to value and is decoupled from society's willingness to pay. No other EU country offers such a "luxury". This price is then the basis for negotiations between the company and the GKV-Spitzenverband on the amount of the reimbursement, which applies from the second year onwards in the market. The absence of market-based price signals for the negotiations gives the price introduced by the manufacturer an influence on the level of the negotiation result. Thus, it is mainly the manufacturers' price expectations that are reflected in the reimbursement amount. In the future, therefore, other informative criteria such as *the* AIM *fair price calculator* should be used.

What is the pricing process according to AMNOG?

Within the first six months of the first marketing of a new medicine with new active substance(s), the Federal Joint Committee (G-BA) carries out an early benefit assessment on the basis of documents (dossiers) to be submitted by the company. This includes the following aspects

- Life extension (mortality),
- Reducing the severity of the disease (morbidity),
- Improved side effect profile (adverse drug reactions) and
- A more favourable *health-related* quality of *life* (HRQoL)

In each case compared to the standard and appropriate comparators (zVT) already available in the German health care context. In addition, the annual costs of the therapy and the number of patients that could potentially be treated with the new drug are determined, which allows the *budgetary impact of the* new therapy option for the GKV system to be estimated. After the G-BA's early assessment of the benefits, the company negotiates with the National Association of Statutory Health Insurance Funds a reimbursement amount that applies from the thirteenth month after market entry. If no agreement is reached between the company and the GKV, an arbitration committee may intervene or the company may choose the option of *withdrawing, i.e. the* company withdraws the medicine from the German market and it is therefore no longer available.

In the case of medicines used for the treatment of rare diseases (*orphan drugs*), i.e. diseases that occur in a maximum of five patients per 10,000 inhabitants in the EU, the G-BA automatically postulates an additional benefit and only determines its extent. Only when a turnover threshold of €50 million is exceeded in a year is the company obliged to conduct a regular benefit assessment (G-BA, 2008; G-BA, 2017c).

The G-BA evaluated 26 of the 31 drugs with new active substances of the year 2019. Twelve of these preparations have an annual therapeutic cost of more than €100,000. This results in an average annual therapeutic cost of €217,313 for the patent-protected drugs evaluated by the G-BA, with *orphan drugs* standing out in particular. By comparison, the average annual therapeutic cost of new drugs in 2010 was 34,253 euros. The prices of new drugs in oncology are also criticized, as data on their incremental benefit at market entry seem incomplete due to increasingly earlier (accelerated) approval (Glaeske et al., 2017). The 2019 cohort illustrates this, as the early assessment of G-BA benefits resulted in the conclusion of "no benefit" or only "unquantifiable additional benefit" for eight out of twelve drugs with oncology indications (Schwabe & Ludwig, 2020).

Therefore, the current system of negotiating GKV-SV reimbursement amounts could be conducted *ad absurdum* by the pharmaceutical company (PU), as possible price reductions to be granted can already be calculated in advance by the company, e.g. based on empirical values in the indication area, in order to achieve a desired market price (Eckert & Osterloh, 2020). The steady increase in market entry prices for new drugs and the results of the negotiations on reimbursement amounts in 2017, with average price reductions on the market entry price of 20%, support this thesis (Schwabe & Ludwig, 2020).

The application of the reimbursement amount from the thirteenth month onwards is another point that deserves to be improved. New gene therapies with very small patient cohorts, which belong to the group of ATMPs (*Advanced Therapy Medicinal Products)*, might already have been used in almost the entire patient population within the first twelve months after market entry, even before the evaluation of the early benefit of the G-BA and the negotiation of a reimbursement amount by the company and the GKV fund are completed. Therefore, in the future, repayment amounts should have a retroactive effect on market entry (Osterloh, 2021). Alternatively, the G-BA could set a provisional price based on the costs of the appropriate comparator (zVT) at market entry until the results of the early benefits assessment are available, as advocated by the GKV-Spitzenverband in its current position paper (GKV-SV, 2021d).

Comparative studies of list prices for patent-protected drugs clearly show that the manufacturer's sales prices in the German Lauer-Taxe database are the highest compared to other European health systems in the EU (Vogler et al., 2018). In their analysis, Busse et al. (2016) arrived at a difference of a GDP-adjusted basket of 16-27%.

One reason for this is that 17 other European countries refer to German list prices in their own pricing (Haas, 2016; Rémuzat et al., 2015) and therefore pharmaceutical companies set higher list prices for Germany, as well as to enter the German market earlier (Vogler Vitry Babar, 2016). Out of 152 new medicines approved in the EU in 2016-2019, 133 (87.5%) were available in Germany, which is the highest rate in the EU (Newton et al., 2021).

Médecins Sans Frontières, Brot für die Welt as well as the parliamentary groups "DIE LINKE" and "Bündnis 90/Die Grünen" have demanded, in the context of a resolution of the World Health Organization (WHO), more transparency in the prices of medicines charged by manufacturers, in particular the disclosure of research *and development* (*R&D)* costs at the time of marketing authorization. In their view, the Federal Ministry of Health (BMG) does not promote this sufficiently. The BMG assumes that the prices of medicines in Germany are sufficiently transparent and refers to the special nature of discounts under Article 130a(8) SGB V, which are to be regarded as business secrets. *Non-governmental organizations* (NGOs), however, warn that negotiations on fair drug prices [and also the amount of discounts on these drugs] can only take place on the basis of transparency (hil, 2019).

The *International Association of Mutual Benefit Societies* (*AIM) has* 57 members from 30 countries in Africa, Europe, Latin America and the Middle East and represents the interests of 240 million people. In Germany, the Joint Representation of Corporate Health Insurance Funds (IKK e.V.), the Knappschaft, the Social Insurance for Agriculture, Forestry and Horticulture (SVLFG) and the Association of Alternative Health Insurance Funds (vdek) are represented (AIM, 2021c). Historically, the roots of the IAM and its predecessor organizations go back to 1906. The IAM was founded on 28 January 1950 (AIM, 2021d). On 4 December 2019, the NGO "AIM" presented its concept for fair pricing of medicines to the European Parliament (AIM, 2019b). It is a computerized online tool1 for wide application and was presented to the public on 11 June 2021 (AIM, 2021a).

1 https://fairpricingcalculator.eu/

In the following, the reasons why AIM has developed a fair price calculator for pricing medicines in the EU are explained, its parameters are presented and the calculator is put to a practical test using selected examples of innovative medicines.

In her presentation on the EU fair price calculator for medicines, Anne Hendrickx of the *Socialist Mutualities of Belgium* first explains the reasons for the need of such a calculation model: strong price increases for new products in the current pharmaceutical market (Bach, 2021), access to new innovative therapies in the EU not possible in all member states at the same time (Newton et al, 2017; Alonso-Zar, 2017), 2021), insufficient R&D investment by pharmaceutical companies (van der Gronde et al., 2017) and performance-driven business models of pharmaceutical companies (Hendrickx, 2021; Alonso-Zaldivar, 2015). An analysis of the top 10 global pharmaceutical companies (PUs) reveals R&D costs of 19% on average, with sales and marketing expenses of 29% and an average return on sales of 20.9%, with the top performer being Pfizer with a return on sales of 43% and the non-top 10 member Gilead with a profit margin of 55% in 2015 (van der Gronde et al., 2017; at, 2016). Hendrickx also cites difficult price negotiations and ambivalent or risky concepts with which negotiating parties pursue conflicting objectives, do not negotiate on an equal footing [due to information deficits], the concept of *value-based pricing* is flawed and the price reduction system is "tricky" and non-transparent. In practice, objective value-based pricing mechanisms are undermined by emotional campaigns [therapy for sick children] and excessive prices are demanded even for *"me-too" preparations*, mostly fake innovations. In practice, the greatest possible health gain with limited budgets is offset by uncertain health gains. Rising prices can lead to a restriction in the use of services in the case of limited health budgets. Based on the willingness *and ability to pay of* EU Member States for innovative products, pricing is based on the principle of "*what the market can bear",* which is also not adapted to the respective gross domestic product (GDP) (Hendrickx, 2021).

According to AIM and Hendrickx, new transparent rules can serve as a solution, in line with the WHO definition of a fair price, i.e. "a price that is affordable for health systems and patients and at the same time provides the pharmaceutical industry with sufficient incentive in the market to invest in innovation and production of medicines". According to Moon et al (2020), this fair price includes the real costs of R&D, production, distribution, marketing authorisation, pharmacovigilance as well as a fair profit (*return on investment (RoI)*). On the part of health insurance funds (often reduced to the role of "payer") and thus also on the part of patients, this means that the medicine can be financed in sufficient quantity, taking into account the security of supply and ultimately the value for the individual and society (Moon et al., 2020). For the EU, Hendrickx assumes a whole and uniform market, i.e. all 27 member states should negotiate jointly with a pharmaceutical company. A reference to the actual costs of the firm should be the basis, and the model would lead to predictability of pharmaceutical expenditure by member states (Hendrickx, 2021).

How does the AIM Fair Price Calculator work?
NGO AIM's algorithm is based on cost and revenue elements and includes the expected number of patients (see Fig. 1). If the company does not plausibly disclose the exact costs, lump sums are taken into account (AIM, 2021b). In this way, the goal of a European price for each new drug approved by the European Medicines Agency (EMA) can be achieved. If necessary, an adjustment to the respective purchasing power can be made by taking into account the respective gross domestic products of the Member States, e.g. for Germany plus 20%.

The Fair Price Calculator is based on four types of disease, namely

- chronic diseases,
- oncological diseases,
- *rare diseases with a prevalence of* <5/10 000 in the EU, and
- very rare *diseases* (*ultra-rare diseases*) with a *prevalence of* <2/100,000.

In detail, five elements are used to calculate the price: the quotient of development costs and the number of treatable patients, production costs, distribution and medical-scientific information costs, a base profit and, if applicable, an innovation bonus (AIM, 2019a).

The global R&D costs are taken into account up to a maximum of 2.5 billion euros, whereby research failures are also recognised and public funding, tax refunds, opportunity costs or company takeovers (buy-outs) are included with clear specifications. If a company does not disclose these costs, a flat rate for R&D costs of EUR 250 million is accepted. The overall development costs are weighted by an EU-27 market share of 35.9% and adjusted to the target population in the area of application (prevalence or incidence) and a treatment rate of 50%. Finally, R&D costs per patient as well as annual therapy costs are derived (Hendrickx, 2021).

If the company discloses its production costs, these are taken into account. Otherwise, lump sums are calculated for:

- Gene or cell therapies 60 000 euros per application,
- Biotechnology orphan drugs 750 euros per month,
- Biotechnology drugs (biological products) 150 euros per month,
- chemically synthesised medicines for the treatment of rare diseases (*orphan drugs*) 250 euros per month
- chemically synthesized active substances 50 euros per month

Which are in turn multiplied by the average duration of therapy. For distribution and medical information, 20% of the R&D costs are taken into account (Hendrickx, 2021; AIM, 2021b).

As a basic profit, the company receives 8% of the total costs; an innovation bonus can be granted and can vary between 5% and 40% of the total costs (see Fig. 2). For this purpose, the improvement in quality of life, extension of *overall survival* (OS) or a progression-free phase of the symptoms of a disease (*progression-free survival,* PFS), curative treatment, unique drug status or indication of the drug in a life-threatening or chronically incapacitating disease are assessed. Therefore, the therapeutic value of the actual innovation is rewarded (Hendrickx, 2021; AIM, 2021b).

If the drug prices determined using this model are compared to the current "PU market prices", the result is a factor of five to ten times lower, from the AIM's perspective (Hendrickx, 2021; AIM, 2021b).

The NGO AIM wants to implement the fair price model step by step. The lack of transparency of costs or of different net prices in the different EU Member States must be replaced by a new transparency. Payers and responsible parties should use the calculator in price negotiations and critically assess the prices proposed by the pharmaceutical company, even outside the EU Member States. In the long term, AIM would like to see pan-European pricing as a prerequisite for access to the European pharmaceutical market. To this end, the company must submit all the necessary data to the EMA as part of the marketing authorisation application; if necessary, an innovation bonus could be recognised by means of a *health technology assessment* (HTA) and finally the price will be decided by the European Commission (Hendrickx, 2021).

Comment: The AIM model is an objective price signal.

By Thomas Ballast, Vice-Chairman of the Board of Directors of Techniker Krankenkasse

Despite highly regulated markets, the prices of new medicines are constantly rising. The AMNOG procedure has so far not been able to stop this development adequately. The AIM *fair price calculator* shows that it is possible to calculate a different price that counteracts the current trend.

Thus, the active substances examined in this study are on average more than twice as expensive as they would be if the *fair price calculator* were applied. The AIM model therefore offers effective starting points for changing the calculation of the current price on the basis of comprehensible and fair criteria. Although the model is still under development, it can already contribute to more objective pricing of new medicines in the short term. In a further development of the AMNOG procedure based on negotiation, it should be taken into account together with other criteria such as *medical necessity,* evidence, security of supply, research in the EU and provision of data for research purposes.

Fig. 1: Input screen of *the* AIM *Fair Price Calculator* (AIM, 2021a) [1]

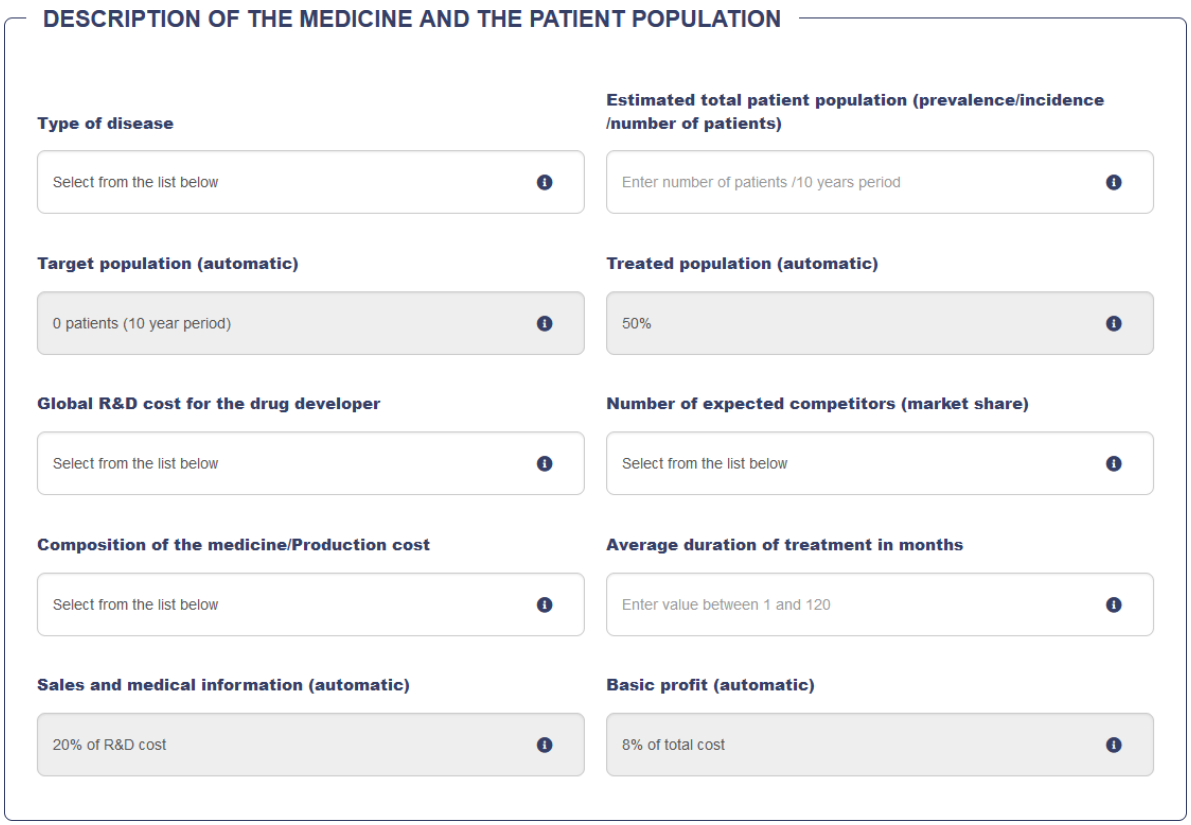
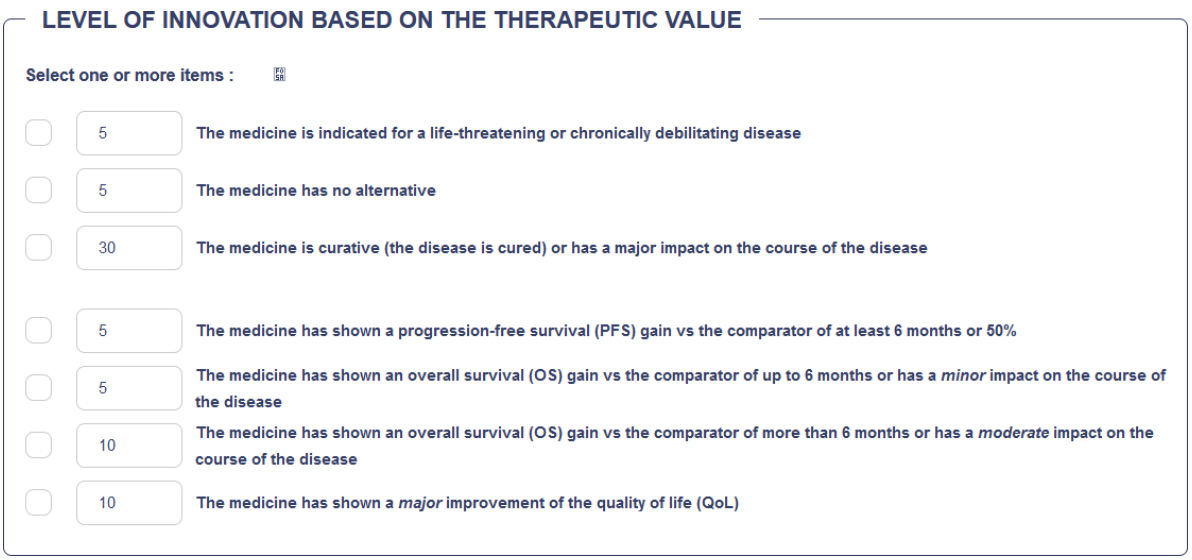


Fig. 2: Input screen 2 of the AIM Fair Price Calculator - Innovation Level (AIM, 2021a)



In the following, the disease types of the AIM calculator are presented on the basis of the drugs evaluated in the innovation reports of the SOCIUM of the University of Bremen. 9

[1] [2] https://fairpricingcalculator.eu/

Orphan drugs or ultra-rare diseases

Onasemnogen-abeparvovec (Zolgensma®)

For the treatment of 5q-associated spinal muscular atrophy (SMA), a progressive neurodegenerative disease, which is differentiated into five subtypes with different degrees of severity (0 to 4) depending on the onset of the disease (in *utero* or in adulthood), various therapeutic alternatives are now available. These include drugs for daily oral administration (Risdiplam (Evrysdi®)), repeated intrathecal injection (Nusiner-sen (Spinraza®)) or single gene therapy (Onasemnogen-Abeparvovec (Zolgensma®)) (G-BA, 2021g; G-BA, 2021f; G-BA, 2017a; EMA CHMP, 2017; EMA CHMP EMA CAT, 2020; EMA CHMP, 2021). The latter was the highest cost drug treatment globally at market launch. Onasemnogen-abbeparvovec offers hope to parents whose newborns with SMA type 1 are at risk of severe disability or even death in the first few years of life if untreated. However, rational evaluation of this treatment option is difficult. The company's emotional marketing with a "lottery" of 100 applications for patients worldwide without medical prioritization based on symptom severity, manipulated preclinical animal test data as part of FDA approval (FDA, 2019), and the acquisition of the publicly funded therapy development company (Beckmann Schillinger, 2020) AveXis for US$8.7 billion raise substantial as well as ethical questions (Kirschner et al., 2020; Naumann-Winter et al., 2020). Onasemnogen abeparvovec is currently only used as an inpatient in specialized centers, with one application. With the entry into the Lauer-Taxe, the German pharmacy price list, on July 1, 2020, only the clinic purchase price of €1,945,000 was therefore published. If the therapeutic costs are calculated with the AIM *Fair Pricing Calculator* using the corresponding parameters, a fair price of 894,457.25 euros is obtained, which is 46% of the current purchase price of the hospital pharmacy. If the German purchasing power is taken into account with a 20 % surcharge, the result is a price of EUR 1 073 348,71 or 55 % of the current price of the hospital EC. The evaluation of the G-BA is currently still in progress (G-BA, 2021f). Thus, no reimbursement amount has yet been negotiated.

[Parameters: ultra-rare disease; SMA type I prevalence 0.17 per 100,000 (G-BA, 2021c); 761 patients in 10 years; 50% treatment rate; R&D costs €250 million; 1 competitor (1/2 of the market) Risdiplam was not yet approved at time of market entry; gene therapy 60.000 per application; sales and medical information costs 20% of R&D costs; base profit 8% of total costs; innovation bonus 35% (fatal disease: 5%; plus major impact on disease progression: 30%)].

Nusinersen (Spinraza®)

Nusinersen (Spinraza®), an *antisense oligonucleotide* for intrathecal (lumbar puncture) use in the treatment of SMA, was launched in 2017. Initially, four doses are given on days 0, 14, 28 and 63, and then maintenance doses are required every four months (120 days), i.e. 34 doses over ten years (EMA CHMP, 2017). In its second decision of 20.05.2021, the G-BA evaluated nusinersen in different subgroups, i.e. according to 5q-SMA type or number of SMN2 gene copies present, after the threshold of 50 million euros in sales was exceeded. For 5q-SMA type 1, he attested to a substantial additional benefit (ZN). For SMA type 2, the G-BA found an indication for a substantial ZN, but for types 3 and 4, a ZN could not be proven. For pre-symptomatic patients with only two copies of the SMN2 gene left, there was an indication for a significant ZN, for three copies of the SMN2 gene an indication for an unquantifiable ZN, but for more than three copies of the SMN2 gene a ZN could not be proved (G-BA, 2021d). 10

In the TK and University of Bremen Innovation Report 2020, Nusinersen was evaluated with two green lights, one for available [new] therapies and one for (additional) benefits. A cost comparison was not performed due to the *orphan drug status (*Glaeske et al., 2020).

The G-BA indicates net GKV costs of €566,745.01 for the first year of treatment, and €261,574.62 per year thereafter, resulting in average costs of €292,091.66 per year over a ten year period. From the second G-BA decision on nusinersen, a minimum prevalence of 1.22/100,000 and a maximum of 1.44/100,000 are calculated. Using the *fair price calculator, a* prevalence of 1.44/100,000 results in a fair price for nusinersen therapy of EUR 21,876.08 or EUR 25,020.29. Taking into account the purchasing power in Germany with a 20% surcharge, the fair price rises to EUR 26,151.30 and EUR 30,024.35 per annum, i.e. 10% and 12% of the current average annual therapy costs (ex-factory), which are defined as a result of the company's free price setting. In the negotiations on the reimbursement amount, the company's price was reduced by about 16 %. Taking the research and development (R&D) costs of USD 30,5 million or EUR 25 656 124 (exchange rate 02.08.2021 1 USD = EUR 0,84) as a basis, the *AIM fair price calculator gives* purchasing power-adjusted annual therapy costs of EUR 7 475,24 or EUR 7 862,45, i.e. about 3 % of the (ex-factory) price currently claimed by the company for one year's therapy.

This example illustrates the great need for transparency in the context of market entry prices for new medicines in the pan-European context.
[Parameters: ultra rare disease; 1.22 and 1.44 patient:in per 100,000 people; 5,460 and 6,444 people treated within 10 years, 50% share; €250 million. R&D costs; 0 competitors (total market); orphan chemical €250/month; 34 applications in 10 years; sales and medical information costs 20% of R&D costs; base profit 8% of total costs; innovation bonus 40%: drug has no alternative [market entry]: 5% plus fatal disease: 5% plus major impact on disease: 30%].

Table 1: Nusinersen (Spinraza®) - *AIM Fair Price Calculator*

AIM Fair Pricing Calculator		
Type of disease	ultra-rare	ultra-rare
Prevalence	1.44 per 100,000	
Target population (automatic)	6,444 pro 10 Jahre	
Treated population (automatic)	50 %	50 %
Global R&D cost for the drug developer	250 Mio. euros	**30.5 Mio. US $ = 25.656.124€**
Number of expected competitors (market share)	0 competitor (total market)	
Composition of the medicine/Production cost	Orphan chemical 250€/Monat	
Average treatment duration [Months].	34	
Sales and medical information (automatic)	20 % der R&D Kosten	
Basis-Profit	8 % der Vollkosten	
Level of Innovation based on the therapeutic value	40 %	
AIM -> Fair pricing components (per treatment per patient)		
R&D cost	27.816,57 €	2.854,66 €
Production cost	8.500,00 €	8.500,00 €
Sales and medical information	5.563,31 €	570,93 €
Basic profit	3.350,39 €	954,05 €
Innovation bonus	16.751,96 €	4.770,24 €
Fair pricing calculation		
Fair pricing per treatment per patient	***61.982,23 €***	***17.649,88 €***
Fair pricing per month of treatment per patient	1.823,01 €	519,11 €
Fair pricing per year of treatment	*21.876,08 €*	*6.229,37 €*
Fair annual therapy costs Adjusted for purchasing power in Germany	**26.251,30 €**	**7.475,24 €**

Chronic diseases

Sacubitril-Valsartan (Entresto®)

The combination of the active ingredients sacubitril and valsartan, already available in generic form (trade name: Entresto®), was approved for the treatment of symptomatic chronic heart failure with reduced ejection fraction and listed for the first time in the Lauer-Taxe in January 2016 (EMA, 2021b). In the early benefit assessment decision of 16.06.2016, the G-BA confirmed an indication of considerable benefit in patients without diabetes mellitus (about 68%), but only an indication of minor benefit in patients with diabetes mellitus (about 32%). The prices of the combination product are tiered by package size (20/56/196 units) regardless of the respective active strength (24/26 mg; 49/51 mg or 97/103 mg), i.e., there is no clear relationship on the part of the company between the price of the finished drug and the costs of the quantity of active ingredient or active strength. The G-BA shows 2,431.91 euros GKV net (16.06.2016) as annual therapeutic costs for a sacubitril-valsartan tablet twice daily. The reimbursement amount reduced the annual therapy costs by 23%. Based on the currently available N3 blister pack of 196 tablets, a unit price of 2.66 euros and a consumption of 730 tablets per year, the annual therapy costs amount to 1,945.15 euros GKV net [as of 15.07.2021].

According to *the* AIM *fair price calculator*, the annual therapy costs of €898.74 to €917.84 are calculated taking into account the purchasing power of the German market (corresponding to a 20% mark-up), which is 56-57% of the current annual therapy costs [EX-USINEX-USINE].

[Parameter: chronic disease; share of patients in population 0.66% or 1.62% [G-BA decision data]; therefore 2,953,500 to 7,249,500 patients within 10 years; treatment rate 50%; R&D cost €250 million; 2 competitors (1/3 of the market); production cost of chemical (€50/month); 120 months of treatment; sales and medical information costs 20% of R&D costs; 8% of total cost as base profit; innovation bonus 15% : Fatal disease 5% plus quality of life improvement: 10%].

Empagliflozin (trade name: Jardiance®)

The renal sodium-glucose *cotransporter* 2 (SGLT 2) inhibitor empagliflozin (trade name: Jardiance®) was approved on 22 May 2014 as the third gliflozin after dapagliflozin and canagliflozin. In the EU, empagliflozin can be prescribed to adults with type 2 diabetes mellitus to improve blood glucose control as monotherapy if diet and exercise are not sufficient or if metformin cannot be used due to contraindications, as well as in combination with oral antidiabetic drugs and insulin. Empagliflozin was first listed in the Lauer-Tax on 15.08.2014. In July 2021, the field of application was extended to the treatment of symptomatic chronic heart failure.
In the first decision of February 15, 2015, the G-BA could not identify any additional benefit for empagliflozin based on the data submitted by the company. In a second procedure based on new studies, five subgroups were distinguished in the decision of 1 September 2016. In monotherapy as well as in combination in patients without or with manifest cardiovascular disease, an additional benefit is not proven (subgroup a), corresponding to 15.2% of patients. In combination with metformin, G-BA was able to demonstrate a minor benefit in patients without cardiovascular disease; in the case of cardiovascular disease, G-BA was able to demonstrate a considerable benefit. In a combination of two drugs with other antidiabetic agents, except metformin and insulin, no additional benefit (ZN) could be proven in patients without cardiovascular disease, but in case of cardiovascular disease there was evidence of considerable ZN. In a triple combination, no ZN could be proven in patients without overt cardiovascular disease; in case of cardiovascular disease, there was again an indication for considerable ZN. The same result was obtained for the combination with insulin, i.e. without cardiovascular disease there was no evidence of ZN, but with cardiovascular disease there was evidence of significant ZN (G-BA, 2016).

The example of empagliflozin impressively shows that pricing based on the benefit to patients in subgroups has to be specific in order to achieve a fair price. The two dosages 10 mg and

25 mg have the same price per package (30 and 100 units respectively), i.e. the company sets a price without any comprehensible link to the actual quantities or costs of the active substance. According to the Lauer-Tax, 25 mg tablets cannot be divided into equal doses, so that a theoretically economic medical prescription with a dosage specification consisting of the company dividing the tablets by two is excluded. Assuming costs of EUR 1.81 per net GKV tablet, this results in annual therapy costs of EUR 659.15 for empagliflozin with a consumption of 365 tablets [Lauer-Tax: 15.07.2021]. The amount of the reimbursement has already reduced the price originally charged by the company by 14%. Using *the* AIM *fair price calculator*, adjusted to the purchasing power in Germany, a fair price for a twelve-month therapy of 861.26 euros to 863.12 euros is obtained, taking into account the corresponding parameters. It is surprising that the fair price is about 65% higher than the current (ex-factory) market price. It should be noted that empagliflozin was the third SGLT2 inhibitor to reach the market and that other standards should be applied to the degree of innovation (see also the so-called me-too preparations). In addition, new signals on the benefit/risk ratio have been issued in the form of warnings ("red hand letters" and information letters) about the risk of occurrence of atypical diabetic ketoacidosis or Fournier's gangrene (AKdAE, 2016; AKdAE, 2019). This raises the question of the extent to which *the* AIM *fair price calculator* could, in the future, take into account "me-too" preparations and the negative effects of new drugs (red letters) for which data are still incomplete.

[Parameters: chronic disease; population share of patients 1.51% or 1.75%; i.e., target population of 6,757,250 or 7,831,250; 50% of population treated; overall R&D cost of 250 million euros; 2 competitors (1/3 of market); production cost of 50 euros per month of chemical; treatment duration of 120 months; sales and medical information costs of 20% of R&D costs; base profit of 8% of total costs; innovation bonus of 10% : corresponding effects only for subgroups, so fatal disease5% plus minor impact on disease5%].

Secukinumab (Cosentyx®)

The fully human monoclonal antibody secukinumab (trade name: Cosentyx®) selectively binds to and neutralizes interleukin 17A, an inflammation-promoting cytokine. Secukinumab received approval for the first indication, plaque psoriasis, in the EU on January 14, 2015, followed by extensions of the indications to psoriatic arthritis, ankylosing spondylitis and axial spondyloarthritis (EMA, 2021a). Biotechnology-produced secukinumab was first listed in the Lauer-Tax on 01.06.2015. In several evaluation procedures for the indication plaque psoriasis, the G-BA gave secukinumab a considerable additional benefit indication in about two thirds of patients; in the Innovation Report 2018, secukinumab also received a green light for (additional) benefit (G-BA, 2017b; Glaeske et al., 2018). On the other hand, the Drug Commission of the German Medical Association warned against a group effect in the use of anti-IL-17A therapeutics in the context of possible induction and/or unmasking of chronic inflammatory bowel diseases (AKdAE, 2018). Secukinumab is administered subcutaneously, weekly (four doses) for the first month, and then a maintenance dose once a month is sufficient, leading to the consumption of 15 doses in the first year and 12 doses per year thereafter, i.e. 123 applications in ten years or an average of 12.3 per year. Secuki-numab is available in pre-filled syringes or in pre-filled pens with 150 mg or 300 mg of active ingredient. Thanks to the reimbursement amount negotiated by the company and the GKV, the price has dropped by 13%. Currently, the costs of a treatment with secukinumab amount to 23,259.95 euros in the first year. (15 applications), now 18,607.96 euros per year, i.e. the average annual therapeutic costs amount to 19,073.16 euros [status: Lauer-Tax: 15.07.2021]. The proportion of the treated population is between 0.07% and 0.33%, i.e. a prevalence of 72.6 to 326.0 per 100,000 in the first approved indication. If all patient groups approved to date are included, the values range from 0.13% to 0.48%, or a prevalence of 155.9 to 550.1/100,000. This difference is particularly important given that the number of patients receiving potential therapy is taken into account in the calculation of a fair price in the AIM *Fair Price Calculator.* The larger the population of potential patients, the lower the fair price. When entering the market without other anti-IL17A therapeutics, such as Ixekizumab or Brodalumab, which are available in the meantime, annual therapeutic costs of EUR 3,113.80 to EUR 3,206.63 per year are obtained, or EUR 3,140.35

to EUR 3,279.14 per year when taking into account competitors and larger patient collectives. Therefore, the fair price of secukinumab therapy is 21% to 22% of the company's current ex-factory price per year.

The example of secukinumab clearly shows that the gradual expansion of areas of application must also be taken into account when calculating a fair price for the drug, at best on the basis of a continuous review of the available evidence, new therapeutic options and new adverse effects.

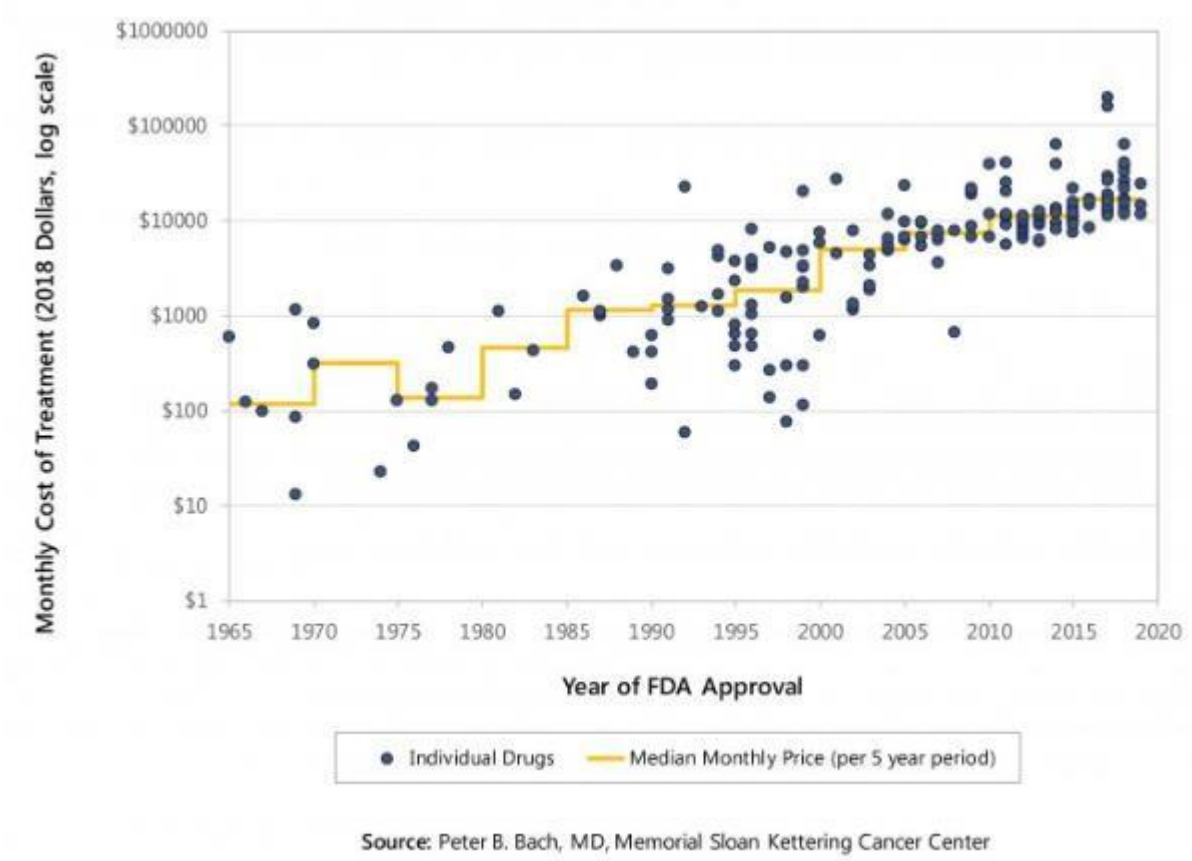
[Parameters: chronic disease; share of patients in population: 0.13% and 0.48%; i.e. target population of 581,750 and 2,148,000; 50% of population treated; €250 million. € global R&D cost; 2 competitors (1/3 of the market); production cost of €150/month of biologics; treatment duration of 120 months; sales and medical information costs of 20% of R&D costs; base profit: 8% of total costs; innovation premium of 35%: life-threatening disease: 5%; curative drug: 30%)].

Oncology

Peter Bach, *Memorial Sloan Kettering Cancer Center*, analyzed the evolution of monthly therapeutic costs for new oncology drugs at the time of FDA approval, which is generally the time of first access to the global market, from 1965 to 2019. Figure 3 illustrates the trend of strong price growth. Whereas in 1965, monthly therapy costs or median monthly costs were still between US$100 and US$1,000, in 2019 costs of around US$10,000 to more than US$100,000 per month for cancer therapy are recorded, with the logarithmic scale to be noted here (Bach, 2021)[4].
In the case of drugs for cancer therapy, the special features of marketing authorisation with increasingly early market entries based on phase I or II studies instead of the previously usual phase III studies must be taken into account, with a consequent situation of disparate data for early benefit assessment. Glaeske and colleagues already addressed this potential for improvement in a paper in 2017 and called for late benefit assessment (Glaeske et al., 2017). In the following, the drug prices of a biotechnology-produced antibody and a conventional combination of chemically synthesized active ingredients are presented as examples.

[4] https://www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs

Fig. 3: "Monthly and median oncology drug costs at FDA approval from 1965 to 2019" modified from Peter Bach MSKCC (2021).



Nivolumab (brand name: Opdivo®)

In the group of immune checkpoint inhibitors (ICIs), the active substances ipilimumab (marketed: 01.08.2011), nivolumab (15.07.2015), pembrolizumab (15.08.2015), atezolizumab (15.10.2017), durvalumab (15.10.2018), and cemiplimab (01.08.2019) are currently available in different and constantly growing areas of application. ICIs indirectly activate the body's T-cell defenses by inactivating the physiological mechanisms that protect against an excessive autoimmune response. As a human monoclonal antibody, nivolumab blocks the *programmed (cell) death-1* receptor (PD-1 receptor) formed on T cells, which prevents the weakening of the PD-L1 or PD-L2 defense on tumor cells (at, 2021).

In the statement of reasons for the decisions on the active substance nivolumab, the G-BA states that the calculation of the annual costs of the therapy is based on the German Medicines Price Regulation (Arzneimittelpreisverordnung) and Annex 3 of the ancillary fee negotiated between the German Pharmacists' Association (Deutscher Apothekerverband, DAV) and the National Association of Statutory Health Insurance Funds (GKV-SV), approximately on the prices of the required pre-packaged medicines plus the cost price (EUR 71 per ready-to-use monoclonal antibody solution). According to the G-BA, it should again be noted that the ancillary price is negotiated continuously and dynamically and that this also results in a lack of transparency.

The G-BA is not aware of any confidential prices below the ancillary prices that may be negotiated between statutory health insurers and compounding pharmacies.

The G-BA has so far conducted 17 assessment procedures for the active substance nivolumab (G-BA, 2021e). In subsequent negotiations between the company and the GKV, the reimbursement amounts resulted in a price 26% below the market entry price.
For simplicity, the annual treatment costs for nivolumab monotherapy at a fixed dose of 240 mg every two weeks, i.e. 26 cycles per year, are calculated. These are EUR 79,308.84 net GKV or EUR 65,799.50 based on the ex-factory price per year. For the price analyses, the costs of producing the infusion solution under aseptic conditions in the pharmacy are not taken into account, but they amount to EUR 1 846 (26 x EUR 71) [Lauer-Tax as of 15 July 2021] (G-BA, 2021b; G-BA, 2021a).

13,825.58 per year for the first approved indication melanoma (ICD-10 C43; incidence according to GEKID6 : 39.3/100,000), taking into account the corresponding parameters. In the indication of malignant pleural aramesothelioma (ICD10: C45.0), which has the lowest incidence of all approved indications, i.e. 2.2/100,000, AIM determines fair annual therapeutic costs of 22,958.58 euros. If, with otherwise identical parameters, a cumulative incidence of 254.9/100,000 is entered into the *fair price calculator*, the fair costs amount to EUR 13,367.50 per year.
As a result, the annual therapeutic costs of nivolumab calculated using *the* AIM *Fair Price Calculator* are three to five times lower than the company's current [ex-factory] market prices.

Table 2: G-BA assessment procedures for nivolumab (n=17) (G-BA, 2021e).

Procedure G-BA	**Start**
Hodgkin's Lymphoma	01.01.2017
Malignant pleural mesothelioma; first line + ipilimumab	01.07.2021
Melanoma	15.07.2015
Melanoma, adjuvant therapy	01.09.2018
Melanoma; combination + ipilimumab	15.06.2016
Melanoma; re-evaluation of adjuvant therapy	01.04.2021
Melanoma; BRAF-V600-WT re-evaluation first line + ipilimumab	15.06.2018
Melanoma; BRAF-V600-WT re-evaluation first line + ipilimumab	15.06.2017
Renal cell carcinoma	01.05.2016
Renal cell carcinoma; first line + cabozantinib	01.05.2021
Renal cell carcinoma; first line + ipilimumab	15.02.2019
NSCLC; combination + ipilimumab + Pt-CT in first line	15.12.2020
NSCLC; non-plaque epithelial histology; after CT	01.05.2016
NSCLC; squamous histology; after CT	15.08.2015
Squamous cell carcinoma of the esophagus; after previous treatment	01.01.2021
Squamous cell carcinoma of the head and neck	01.06.2017
Urothelial carcinoma	01.06.2017

[5] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/272/
The example of nivolumab highlights the complexity of assessing the benefit of drugs with new or known active substances when the marketing authorisation is extended to new indications, as well as their pricing. With increasing use, the company's revenues increase on the one hand and, on the other, fixed costs also become lower due to economies of scale. A continuous adjustment of the evaluation and also the pricing of costs and benefits in the whole patient population seems necessary and urgent. In addition to the "early" assessment of benefits according to AMNOG, a solution should be sought in the form of a continuous assessment based on the best possible evidence and a resulting "dynamic" price.

[Parameters: cancer; 39.3/100,000; 1,758,675 patients in 10 years; treatment rate of 50%; R&D costs of €250 million; 2 competitors (2/3 of the market); biological production cost of €150; treatment duration of 60 months; sales and medical information costs of 20% of R&D costs; base profit of 8% of total cost; innovation premium of 15%: life-threatening disease of 5% and OS gain of more than 6 months of 10%.]

Trifluridine/Tipiracil (trade name: Lonsurf®)

The combination of the nucleoside analogue trifluridine with the thymidine phosphorylase inhibitor tipiracil (trade name: Lonsurf®) was approved on 25 April 2016 for the treatment of metastatic colorectal carcinoma (mCRC) in the EU as monotherapy in patients who were already receiving available drugs or who cannot receive them due to contraindications. In 2019, use in metastatic gastric cancer was added, which also includes gastroesophageal junction adenocarcinoma (EMA, 2016). In mCRC, the G-BA certified an indication for low ZN in two evaluation procedures, in the second indication only an indication for low CN based on an *overall* survival (OS) prolongation of 2 and 2.1 months, respectively. *Progression-free* survival (PFS) was prolonged by 0.2-0.4 months depending on the study, health-related quality of life data were not submitted by the company, and more severe CT-CAE grade ≥3 adverse drug reactions (ADRs) were observed (G-BA, 2020). In the 2019 Innovation Report, the combination formulation received yellow traffic lights (Glaeske et al., 2019).
The annual therapy costs amount to 43,985.80 euros GKV-net or 35,099.96 euros (ex-factory) [Lauer-Tax with price as of 15.07.2021]. In the course of negotiations on the amount of the refund, there was a price reduction of 35% (ex-factory). On the basis of the findings of the Centre for Cancer Registry Data of the Robert Koch Institute (RKI, 2021), the AIM *Fair Pricing Calculator* results in annual treatment costs of EUR 1 196.50 to EUR 2 689.20, i.e. 3.5% to 7.7% of the price currently calculated by the company (ex-factory), taking into account the relevant parameters. As a result, the company is requesting a 13 to 29 times higher price in the ex-factory to AIM comparison.

[Parameter: Cancer, incidence per year 22.2 mGCA/83.2 mCRC/all indications 105.4; 10-year target population 993,450/3,723,200/4,716,650; 50% of population treated; €250 million global R&D costs; 0 competitors; production costs €50/month; average treatment duration two months; sales and medical information costs 20% of R&D costs; base profit 8% of total costs; innovation premium 10% : Potentially fatal disease: 5% plus OS gain up to 6 months: 5%].

The example of the trifluridine/tipiracil combination preparation shows that the price of oncology drugs is detached from the actual production costs and that an assessment of benefit and price should be carried out on an ongoing basis, i.e. reimbursement amounts should be dynamically adjusted to the state of evidence.

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Conclusion

Three cases in recent years are alarming in the context of the free pricing of medicines by pharmaceutical companies and illustrate the dubious business practices of the respective players. The question arises of a price assessment already at the time of approval as well as a continuous monitoring of drug prices with an internal and external reference price system similar to that of other countries such as the Netherlands or Austria.

Specifically, this is the case of a former hedge fund manager who acquired the marketing rights to the generic active ingredient pyrimethamine (Daraprim®) and increased its price from US$13.50 to US$750 per tablet, or by more than 5,555% (Sucker-Sket, 2018).

The company Aspen Pharma, after acquiring the licenses for generic active ingredients for cancer therapy, increased their prices by 300% above the relevant costs in the EU. Aspen Pharma was unsuccessful in an EU antitrust case and was forced to supply the drugs for five years, as well as price reductions and a binding price cap for ten years (Sucker-Sket, 2021). As a result, there is already a governmental and even European definition of pharmaceutical sales prices.

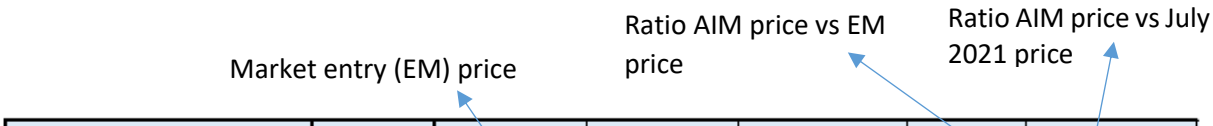
With a market entry price of 700 euros per tablet or 60,000 euros per course of therapy for the drug sofosbuvir (Sovaldi®), the company Gilead has initiated a discussion on the solidarity-based financing of the health system and the GKV in Germany. If all patients with hepatitis C infection had been treated with sofosbuvir in the first year after it was marketed, costs amounting to two thirds of the annual drug expenditure would have been incurred. The question of the relationship between production costs, in the case of sofosbuvir around EUR 100 for a treatment course, and the market entry prices freely chosen by the company, in this case EUR 60 000, has therefore been widely discussed. Gilead's profit margin of 55% in 2015 supports the call for a transparent pricing model that accounts for real production costs and limits profit margins (Iyengar et al., 2016; La-schet, 2014; Ziegler, 2014a; Ziegler, 2014b).

Overall assessment

The concept of fair pricing of medicines and its implementation in the form of *the* AIM *Fair Price Calculator* is an enrichment in this context. It explicitly addresses the issue of appropriate market entry prices for new medicines with patent-protected active ingredients, i.e. prices determined on the basis of transparent full cost calculations. It is used on a daily basis in negotiations with pharmaceutical companies on the price of medicines, providing arguments for payers and encouraging pharmaceutical companies to be more transparent.

The annual therapeutic costs calculated as an example and the comparison with current costs show that political action is absolutely necessary.

Table 3: Comparison of annual therapeutic costs of innovative medicines based on ex-factory price at market entry or current ex-factory (as of July 15, 2021) vs. ex-factory price of the AIM Fair Pricing Tool adjusted for purchasing power in Germany



INN	FAM	Markteintritt (MA)	15. Jul 21	AIM Fair Pricing	Verhältnis AIM vs MA	Verhältnis AIM vs Juli 2021
Onasemnogen-Abeparvovec	Zolgensma	1.945.000,00 €	1.945.000,00 €	1.073.348,70 €	1,8	1,8
Nusinersen	Spinraza	304.640,00 €	256.609,90 €	30.024,35 €	10,1	8,5
Sacubitril-Valsartan	Entresto	2.007,50 €	1.599,78 €	917,84 €	2,2	1,7
Empagliflozin	Jardiance	616,85 €	523,56 €	863,12 €	0,7	0,6
Secukinumab	Cosentyx	18.588,16 €	15.187,50 €	3.279,14 €	5,7	4,6
Nivolumab	Opdivo	88.920,00 €	65.799,50 €	13.367,50 €	6,7	4,9
Trifluridin/Tipiracil	Lonsurf	54.220,83 €	35.099,96 €	2.689,20 €	20,2	13,1

With the exception of empagliflozin, current annual therapeutic costs are two to 13 times higher, and relative to market entry two to 20 times higher, than they should be according to fair criteria. The company should explain how this discrepancy is occurring.

If we analyse the reductions in drug prices achieved through negotiations on reimbursement prices compared to the situation at market entry, we find that they range between 13 and 31%. In 2016, Busse and colleagues had already determined that prices of patent-protected drugs in Germany had increased by 16-27% for a basket of goods in a European comparison adjusted for purchasing power (Busse et al., 2016). This leads to the question of how relevant the concessions made by the company in negotiating the reimbursement amount are given the higher market prices in Germany.

Using *the* AIM *fair price calculator*, the annual therapeutic costs are reduced by 45-95% compared to those claimed at market entry (ex-factory). It should be noted here that the NGO AIM also considers production costs in calculating a fair price for the drug and scales the profit margin, i.e., 8% base profit plus an optional innovation bonus of up to 40%, depending on the evidence of benefit. Excludes profit margins for pharmaceutical wholesalers and pharmacies.

Table 4: Percentage Price Reduction vs. AIM *Fair Price Calculator* Effect

INN	FAM	Preisreduktion durch Erstattungsbetrag GKV-Netto	Preisreduktion AIM APU Markteintritt
Onasemnogen-Abeparvovec	Zolgensma	NN	45%
Nusinersen	Spinraza	16%	90%
Sacubitril-Valsartan	Entresto	23%	54%
Empagliflozin	Jardiance	14%	-40%
Secukinumab	Cosentyx	13%	82%
Nivolumab	Opdivo	26%	85%
Trifluridin/Tipiracil	Lonsurf	31%	95%

Price reduction due to net GKV refund amount

Ex-factory AIM price reduction/ Market entry

The sales of the Zolgensma-free drugs selected for this article amounted to €1.212 billion, or 5.9% of the GKV expenditure for drugs with patent protection (€20.637 billion net GKV) in 2019 (Schwabe & Ludwig, 2020). Using the sales of DDDs by Central Pharma Number (PZN) in 2019, it is possible to calculate the costs that would have been incurred if the fair AIM prices had been used (Fricke et al., 2021; WIdO, 2021). These represent a total of approximately €444 million in the sample, or a potential saving of 63.34% of expenditure in 2019. For the GKV patented drugs segment, this would represent a saving of around €13 billion.

Table 5: Potential GKV savings for innovative substances using *the* AIM *fair price calculator* on selected examples at the current ex-factory price [Lauer-Tax as of 15.07.2021]

INN	FAM	Ausgaben GKV netto 2019	Ausgaben GKV bei AIM-Preis 2019	Einsparpotenzial GKV Preise 15.07.2021	Einsparpotenzial GKV Preise 15.07.2021 [%]
Onasemnogen-Abeparvovec	Zolgensma	NN		NN	
Nusinersen	Spinraza	13.729.200 €	1.571.137 €	12.158.063 €	88,56%
Sacubitril-Valsartan	Entresto	186.611.500 €	86.421.551 €	100.189.949 €	53,69%
Empagliflozin	Jardiance	198.084.200 €	221.467.133 €	-23.382.933 €	-11,80%
Secukinumab	Cosentyx	336.341.700 €	51.255.204 €	285.086.496 €	84,76%
Nivolumab	Opdivo	453.619.400 €	82.197.307 €	371.422.093 €	81,88%
Trifluridin/Tipiracil	Lonsurf	23.807.800 €	1.497.111 €	22.310.689 €	93,71%
		1.212.193.800 €	**444.409.443 €**	**767.784.357 €**	**63,34%**
GKV- Patent-AM netto		20.637.000.000 €		13.071.148.992 €	63,34%

Net GKV expenditure 2019

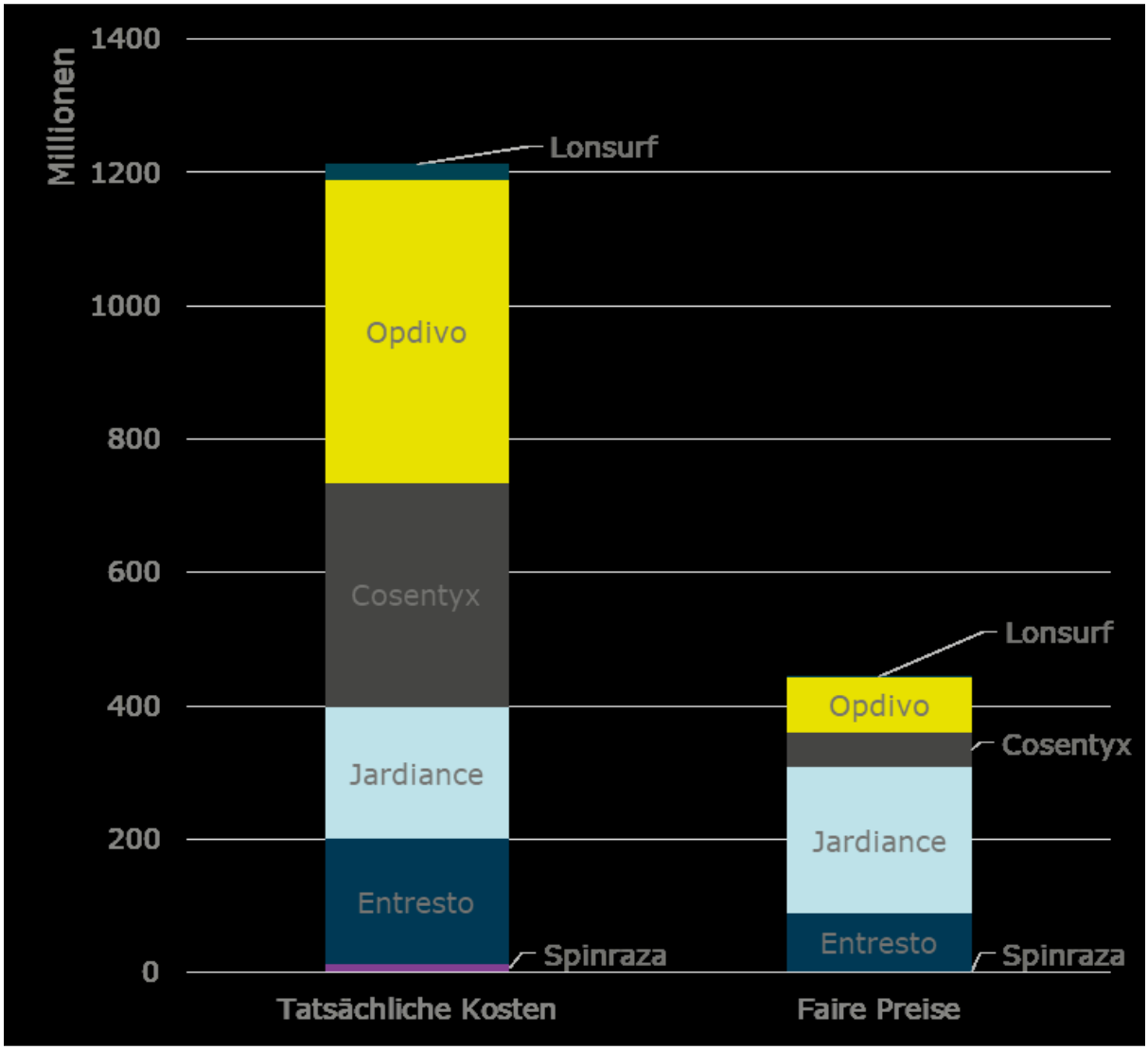
GKV expenses at AIM 2019

Potential savings GKV price 15.07.2021

Savings potential GKV price 15.07.2021 [%]

Overall, the AIM *fair price calculator* can be considered a useful addition. However, the details of the decisions and the reasons behind a G-BA benefit assessment according to Article 35a SGB V can only be presented in limited complexity. In the case of multiple extensions of indications (e.g. nivolumab) or "me-too" preparations, the results of the *fair price calculator* must be evaluated accordingly. However, it should be evaluated as a learning system; many aspects of the price calculator certainly need to be reconsidered and readjusted. Nevertheless, this approach to pricing can be understood as a call to pharmaceutical companies to offer more transparency in pricing, as only then can price negotiations be conducted on a more realistic basis than today - in the interest of European health systems and thus of health insurance funds and their policyholders, but also to further develop trust in the willingness of pharmaceutical companies not to financially overburden health systems. Therefore, the AIM proposal should be taken into account as a reason for urgent discussion. 21

Fig. 4: Comparison of net GKV expenditure in 2019 with hypothetical expenditure under fair AIM prices.



Current costs Fair price

Appendix :
The "Fair Pricing *Calculator*" of the NGO AIM takes into account ten parameters to describe the drug and the patients who can be treated with it:

1. the nature of the disease
2. the number of patients
3. the worldwide research and development (R&D) costs for the "developer" of the drug.
4. galenicals, i.e. the composition of the drug and the production costs
5. distribution and medical-scientific information
6. estimated number of patients within 10 years (prevalence/incidence/number)
7. treated patient group
8. the number of competitors in the market, i.e. the dynamics of competition or the refinancing of R&D
9. Average duration of treatment in months
10. basic profit rate of the pharmaceutical contractor

The definition of the degree of innovation of a new drug is based on the therapeutic value using seven parameters:

1. life-threatening or chronically debilitating disease
2. no therapeutic alternatives
3. possibility of curative treatment or significant influence on the course of the disease
4. a gain of at least six months or 50% in progression-free survival (PFS) over comparator therapy.
5. gain of up to six months overall survival (OS) over comparator therapy, or influence of six months or less on disease progression.
6. gain of more than six months in overall survival (OS) over comparator therapy or moderate impact on disease progression.
7. significant improvement in quality of life

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Added to the translation:

Glossary

KJ1 statistics: reporting on the statutory health insurance fund of the German Ministry of Health

GKV: statutory (as opposed to private) health insurance

Lauer-Taxe database: reference database of medicinal product prices in Germany

zVT: standard and appropriate comparator used in AMNOG (the German law on the reorganization of the drug market introduced in 2011)

ZN: additional profit

PU: pharmaceutical company

APU: ex-factory price

PZN: Central