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Drastic changes in Europe's 1st launch country: How recent legislative changes impact the German P&R landscape

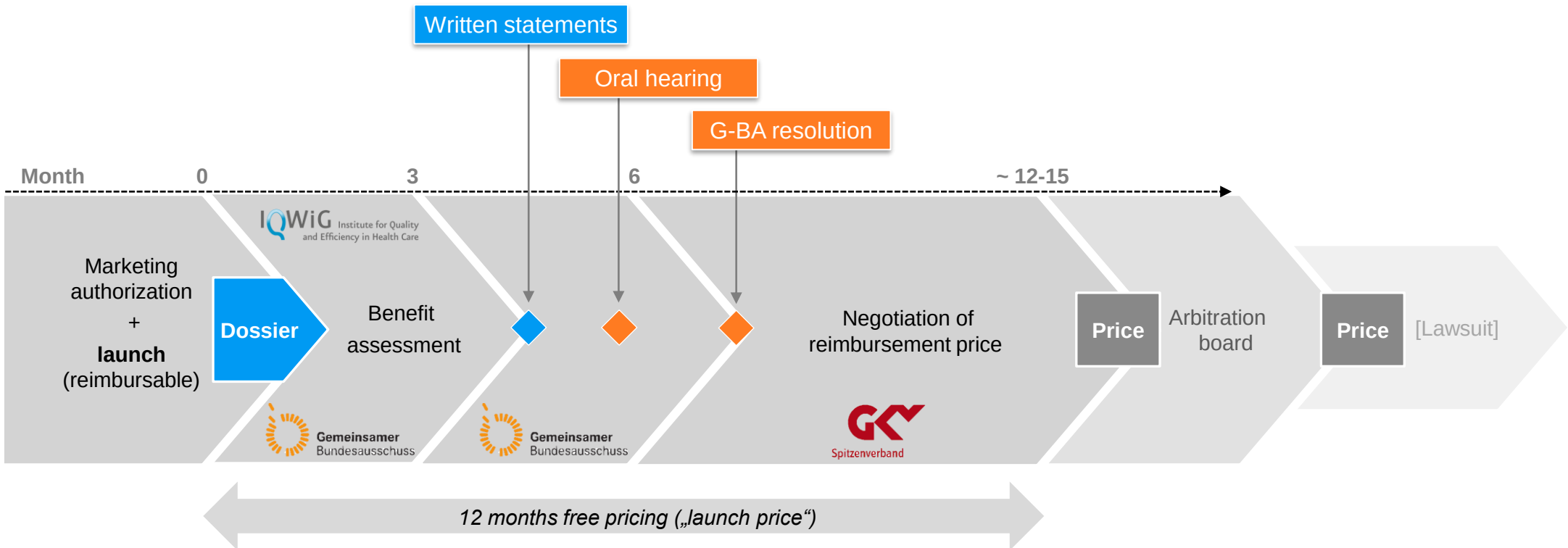
Hamburg, March 15th, 2023

GKV-FinStG, BSG and Beyond
EUCOPE Webinar on March 15th, 2023

Agenda

Early benefit assessment – from dossier submission to price negotiations

Negotiation of a good reimbursement price as final goal



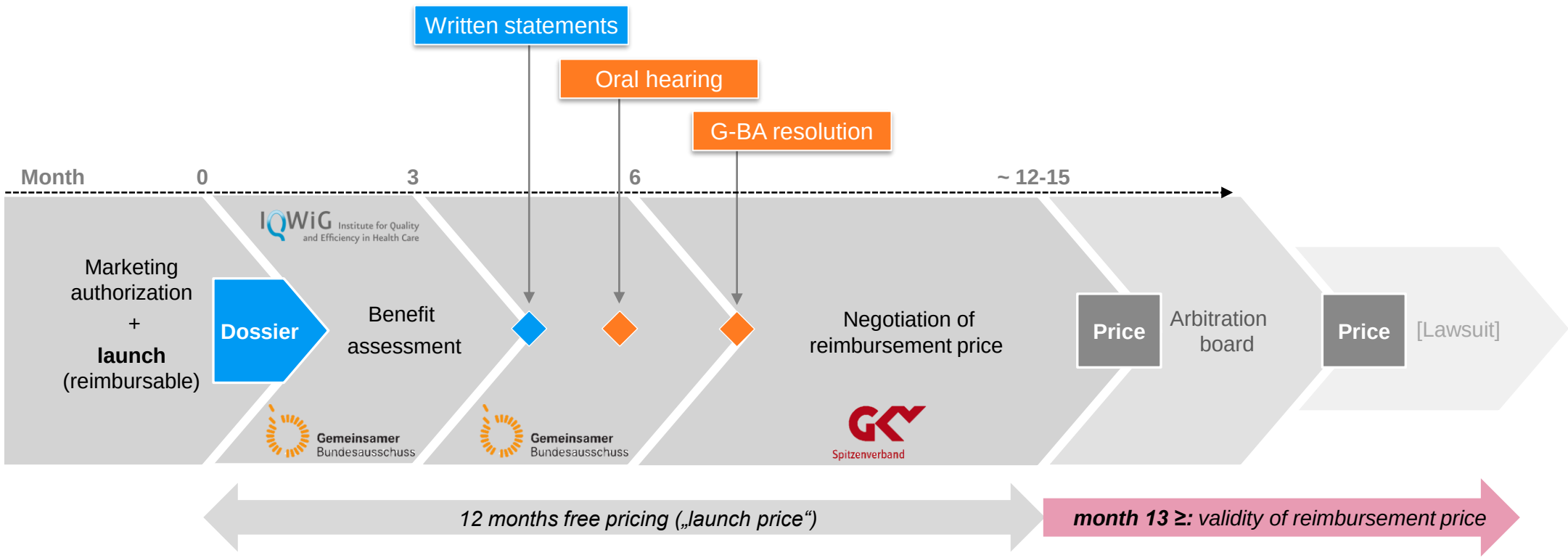
G-BA: *Gemeinsamer Bundesausschuss* (federal joint committee). GKV-Spitzenverband: national association of statutory health insurance

Agenda

Agenda

Early benefit assessment – from dossier submission to price negotiations

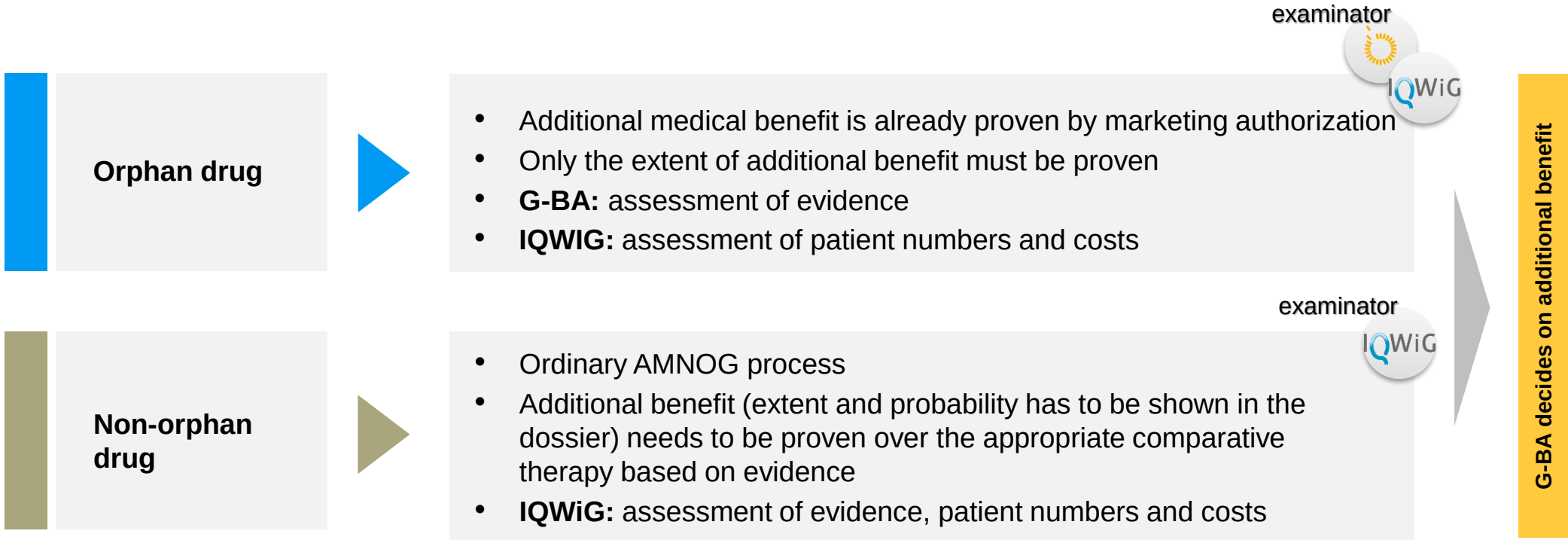
"The old world" before the SHI Financial Stabilization Act ("GKV-FinStG") entered into force



G-BA: *Gemeinsamer Bundesausschuss* (federal joint committee). GKV-Spitzenverband: national association of statutory health insurance

Special status of orphan drugs during benefit assessment

"The old world" – and still valid with the SHI Financial Stabilization Act

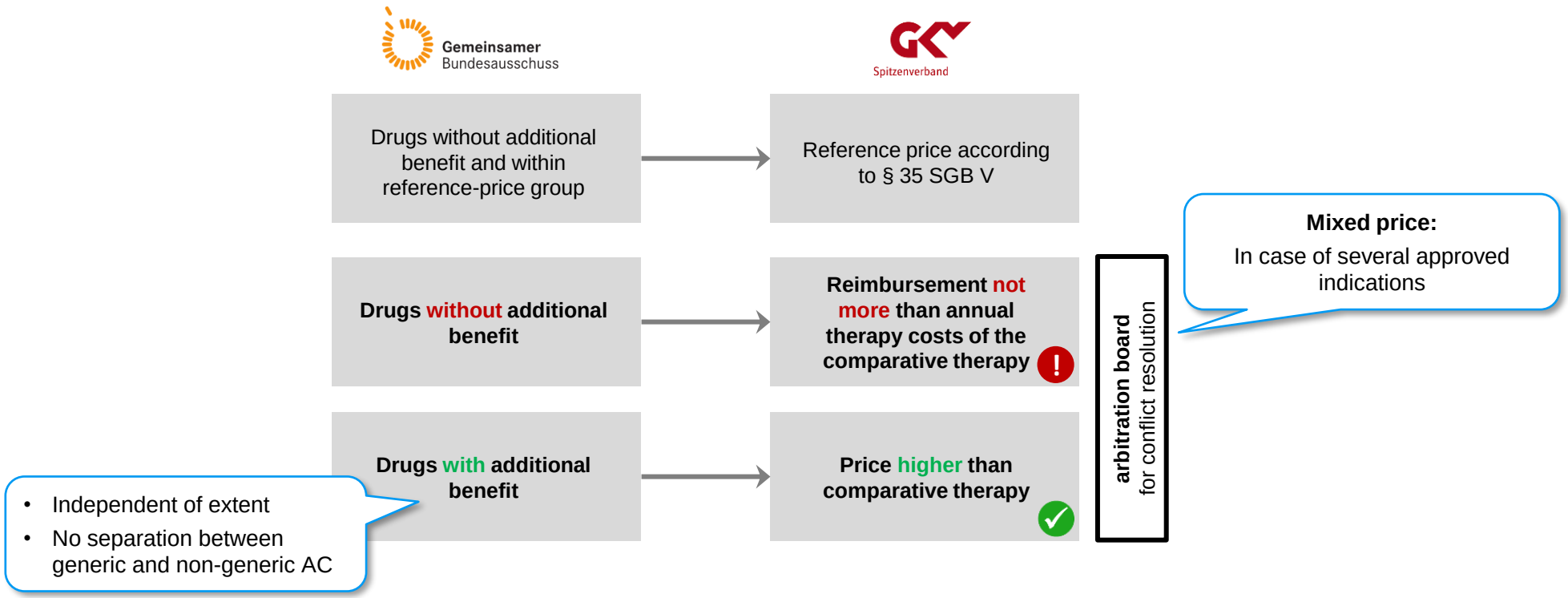


G-BA (Gemeinsamer Bundesausschuss): Federal Joint Committee; AMNOG: Arzneimittelmarktneuordnungsgesetz (Pharmaceutical Market Restructuring Act); IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)

Maximal reimbursement price is based on results of benefit assessment

"The old world" before the SHI Financial Stabilization Act entered into force

- **General idea: „Real" innovation should get a fair price**
- New pharmaceutical products that do not show any benefit in comparison to existing standard therapy should not be more expensive



AC: Appropriate comparator

The SHI Financial Stabilization Act ("GKV-FinStG") changed some of the rules

Main 10 changes

With the plenary session on October 28th 2022, the Federal Council ("Bundesrat") gave its final approval to the legislative changes made by the SHI Financial Stabilization Act which entered into force on November 12th 2022

1 **Orphan Drugs**
Turnover threshold for full evaluation for Orphans at €30 million

2 **Price negotiation**
Reimbursement price valid from 7th month onwards

3 **Price negotiation**
Mandatory price-quantity scale or total volume

4 **Price negotiation**
AC under patent or document protection

5 **Price negotiation**
AC or comparable med. product patent-protected and without benefit assessment

6 **Price negotiation**
Consideration of waste

7 **Price negotiation**
Special termination right of the reimbursement price contract for 3 months (both parties)

Till February 1st, 2023

8 **Mandatory rebates**
Increased mandatory rebate for 2023

9 **Mandatory rebates**
Price moratorium until 2026

10 **Mandatory rebates**
Combination discount of 20 % as payback

AC: Appropriate comparator

And these changed rules should lead to significant annual savings for the statutory health insurances

In total: ~ € 2-3 billion

1 **Orphan Drugs**
Turnover threshold for full evaluation for Orphans at €30 million
→ € 100 million

2 **Price negotiation**
Reimbursement price valid from 7th month onwards
→ € 150 million

3 **Price negotiation**
Mandatory price-quantity scale or total volume
→ € 50 – 100 million

4 **Price negotiation**
AC under[illegible]t or document protection
5 **Price negotiation**
AC or comparable med. product patent-protected and without benefit assessment
New guard rails (cf. following slides)
→ € 250 – 300 million

6 **Price negotiation**
Consideration of waste
New guard rails (cf. following slides)
→ € 50 million

8 **Mandatory rebates**
Increased mandatory rebate for 2023
→ € 1 billion

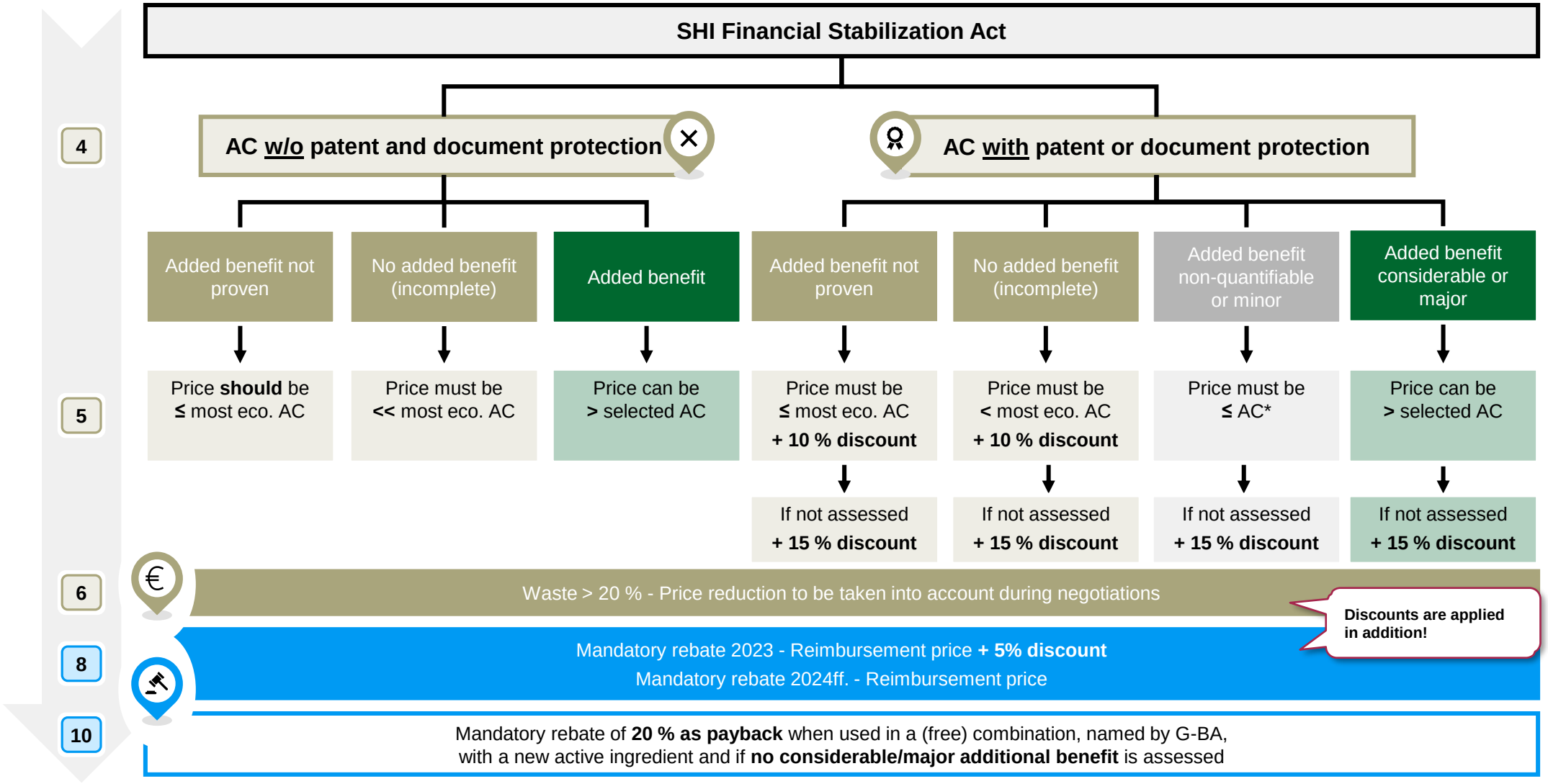
9 **Mandatory rebates**
Price moratorium until 2026
→ € 50 million

10 **Mandatory rebates**
Combination discount of 20 % as payback
→ € 185 million
New guard rails (cf. following slides)

AC: Appropriate comparator

Agenda

5 out of these changes have an direct impact on the reimbursement price negotiation



*) This probably means the most economical appropriate comparator (is not explicitly stated in the new § 130b para. 3 sentence 5 social code book V)
AC: Appropriate Comparator

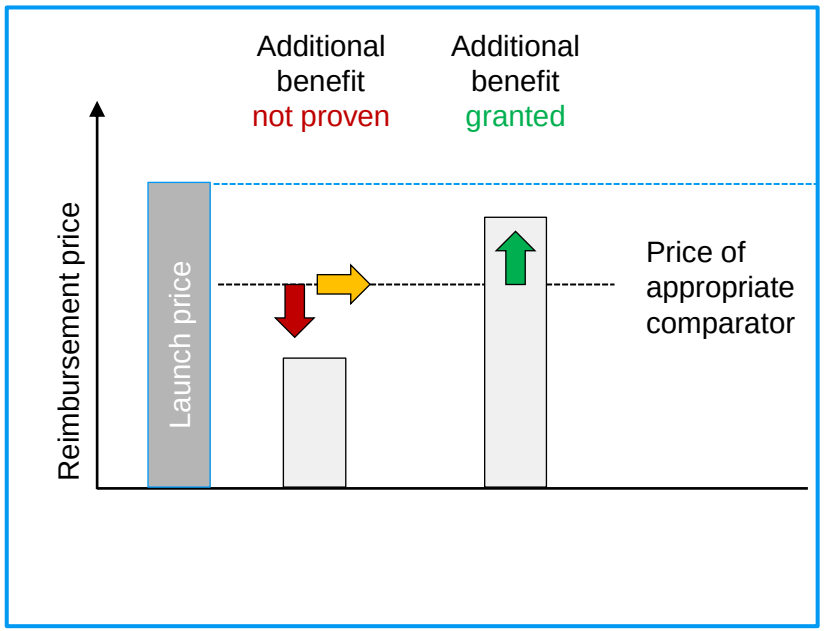
To put it in a nutshell: The SHI Financial Stabilization Act changes the price anchors for a newly launched product significantly to the detriment of the pharmaceutical manufacturers

4

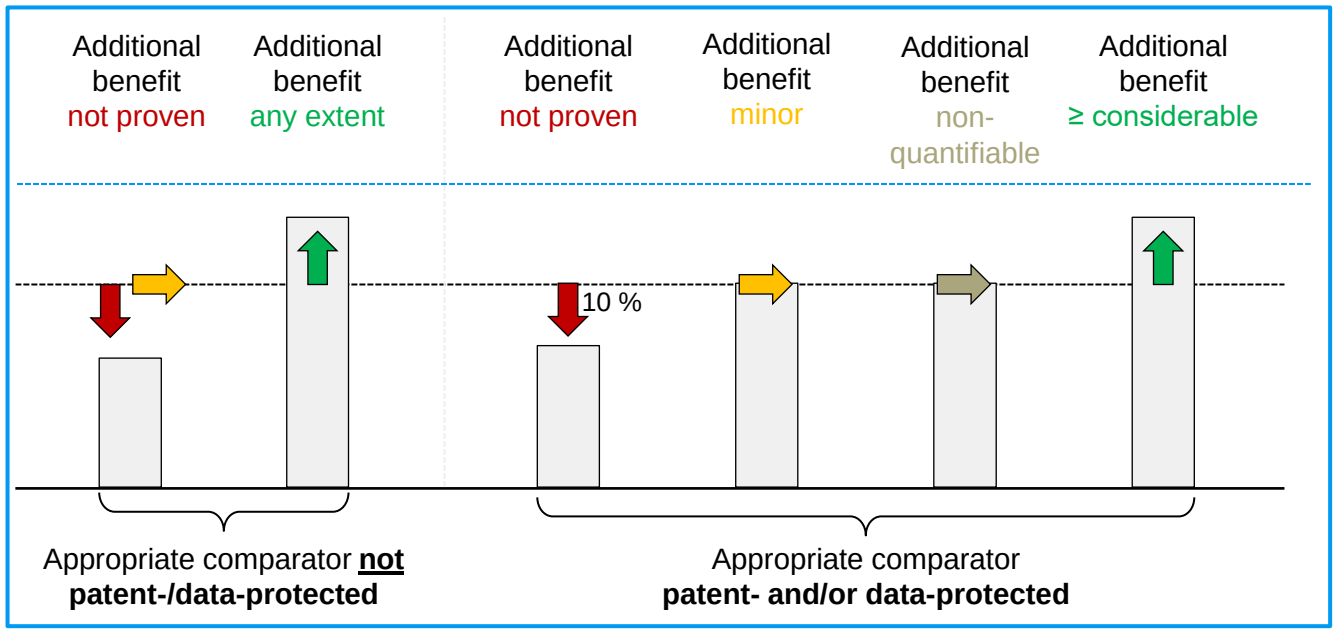
Price negotiation

AC under patent or document protection

Outdated law



SHI Financial Stabilization Act



The pressure on the pharmaceutical company for the reimbursement price increased significantly!

In addition, the new guard rails for the reimbursement price entail open questions and challenges if an individual therapy is defined as appropriate comparator

Consists often of both, patented/non-generic and generic drugs

1. **Additional benefit of the medicinal product in relation to the appropriate comparator therapy**

Adults with symptomatic chronic heart failure with preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

Appropriate comparator therapy for empagliflozin:

An optimised standard therapy for the treatment of symptomatic chronic heart failur with preserved ejection fraction or mildly reduced ejection fraction and the underlyin conditions, such as hypertension, arrhythmias, coronary artery heart disease, diabete mellitus, chronic kidney disease, dyslipoproteinaemia as well as the concomitan symptoms

Extent and probability of the additional benefit of empagliflozin compared wit optimised standard therapy for symptomatic chronic heart failure with preserve ejection fraction or mildly reduced ejection fraction and underlying conditions:

Hint for a minor additional benefit

1. **Additional benefit of the medicinal product in relation to the appro therapy**

a) Adults with unresectable or metastatic gastric cancer with micros high (MSI-H) or with mismatch repair deficiency (dMMR) and disea or following one prior therapy

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of pembrolizumab compared to the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit

c) Adults with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14-) skipping following first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy

Appropriate comparator therapy for tepotinib as monotherapy:

Patient-individual therapy, taking into account previous therapy and histology with selection of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab and docetaxel in combination with nintedanib and vinorelbine.

Extent and probability of the additional benefit of tepotinib compared to the appropriate comparator therapy:

An additional benefit is not proven.

Usually, those appropriate comparators are considered as „basket“

Open questions

Scenario additional benefit not proven or non-quantifiable/minor additional benefit

- What is the most economical appropriate comparator in case of *patient-individual therapy*, *therapy according to doctor's instructions* or *optimized standard therapy*?
- **Are new guard rails** (especially additional discount of 10 %) **applicable** to these defined appropriate comparators?
- **If yes, at which stage?** Only on all/selected drugs with data/patent protection? Or on basket price?

Free combination therapies with new compounds but without at least a considerable additional benefit are affected by a discount of 20 % (“combination discount”) as payback

Target of law change

- AMNOG drugs in free combination with other medicinal product with data protection (“new compounds“) according to the respective label
- Pharmaceutical manufacturers can submit application for exemption from “combination discount“ to Federal Joint Committee (“Gemeinsamer Bundesausschuss“/G-BA)

Determination of combination therapies with new compounds

- G-BA determines – even retroactively – combination therapies of new compounds (so far, no combination therapy with new compounds were identified)
- Application for exemption of combination discount: G-BA evaluates for combination therapies with new compunds if at least a considerable additional benefit is expected ⟶ G-BA Rules of Procedure *(“Verfahrensordnung“)* are currently adapted for application procedure

Sick funds will be authorized to use patient-related health claim data*
(“Sozialdaten bei den Krankenkassen”)

“Combination discount“

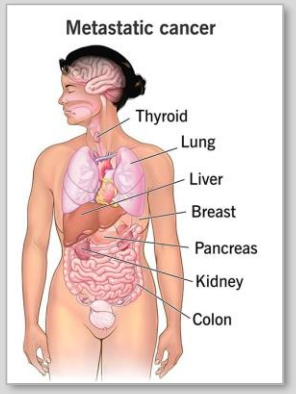
- Sick funds obtain an additional discount of 20 % on ex-factory/reimbursement price **of each manufacturer**
- **Combination therapy** shows **considerable or major additional benefit** (concluded by G-BA): Pharmaceutical manufacturers **are exempt** from payment
- Combination discount is **considered as payback** for the individual sick fund, **no visible discount or price decrease**
- Sick funds and manufacturers (or their respective associations) must set up a specimen agreement for the technical implementation of the payback procedure till 1 May 2023

*) Section 284 paragraph 1 sentence 1 point 8 in conjunction with paragraph 3 sentence 1 of the German Social Code V

Although sick funds are now authorized to use patient-related data, there are treatment constellations which can be in principle misidentified as combination therapy

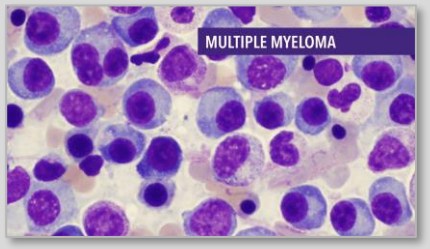
Examples: Patient with 2 forms of cancer or patient with change of medication

Hypothetical examples!



Patient with

- **Melanoma** ⟶ Treatment with nivolumab (Opdivo®) mono therapy
- **AND Renal cell carcinoma (RCC)** ⟶ Treatment with cabozantinib (Cabometyx®) mono therapy *or*
- Also possible for RCC: Combination therapy nivolumab + cabozantinib



Patient with Multiple Myeloma

- Treated with daratumumab (Darzalex®) monotherapy
- Change of medication to carfilzomib (Kyprolis®) + dexamethasone e. g. due to intolerance

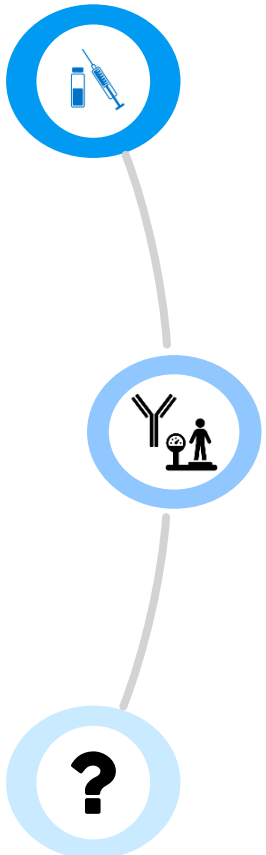
!

Potential misidentification of triple therapy carfilzomib + daratumumab + dexamethasone

?

Major challenge: Distinction between mono therapy, combination therapy (1st example) and change of medication (2nd example) even possible? How are misidentifications avoidable? ⟶ Treatment lines, intolerances of patients are (so far) not available in data…

Administration of AMNOG drugs associated with a reject ("waste") of ≥20 % leads to an additional – but not further specified – decline of the negotiated reimbursement price



"Waste" discount

- If AMNOG drugs with "uneconomical" package sizes cannot be administered with a therapy-appropriate dosage *AND* **their administration is expected to lead to a reject ("waste") of ≥20 % of the content** (e. g. per vial), a **further discount** ("waste discount") on **the negotiated reimbursement price depending on the occuring waste** has to be considered
- No payback, direct impact on reimbursement price ⟶ **Visible price decline!**

Target of law change

- I. a. monoclonals antibodies in oncological and non-oncological diseases, cytostatic drugs, enzyme replacement therapies
- Relevant especially for AMNOG drugs with
  - parenteral application (e. g. vials, syringes etc.) and
  - dosage depending on body weight and/or body surface

Open questions: Determination of waste and impact on reimbursement price

- **Data base** for determination of potential/expected **waste** is **not clear** ⟶ Body weight and size of real patient **is not available** for sick funds
- Determination on German standard patient (1.72 m, 77.0 kg)? Drug dosage on prescription by physician? Settlement of the pharmacies according to "Hilfstaxe"-agreement? ⟶ Latter option works only for drugs subject to this agreement!
- **Correlation between waste and "waste discount"?** 21 % waste ≙ 21 % *or* 1 % *or* X % additional discount?

Agenda

Marketing authorization vs. benefit assessment for orphan drugs

Marketing Authorization

Orphan drugs receive incentives for marketing authorization

Requirements:

- Life-threatening or chronically debilitating
- Prevalence of the condition in the EU must not be more than 5 in 10,000
- No satisfactory treatment existing

Market exclusivity

Benefit Assessment

Orphan drugs receive incentives for benefit assessment in Germany

Requirements:

- Orphan drug status given by EMA
- Revenues from the pharmaceutical have to be below € 30 million over the past 12 months

Additional benefit granted by law

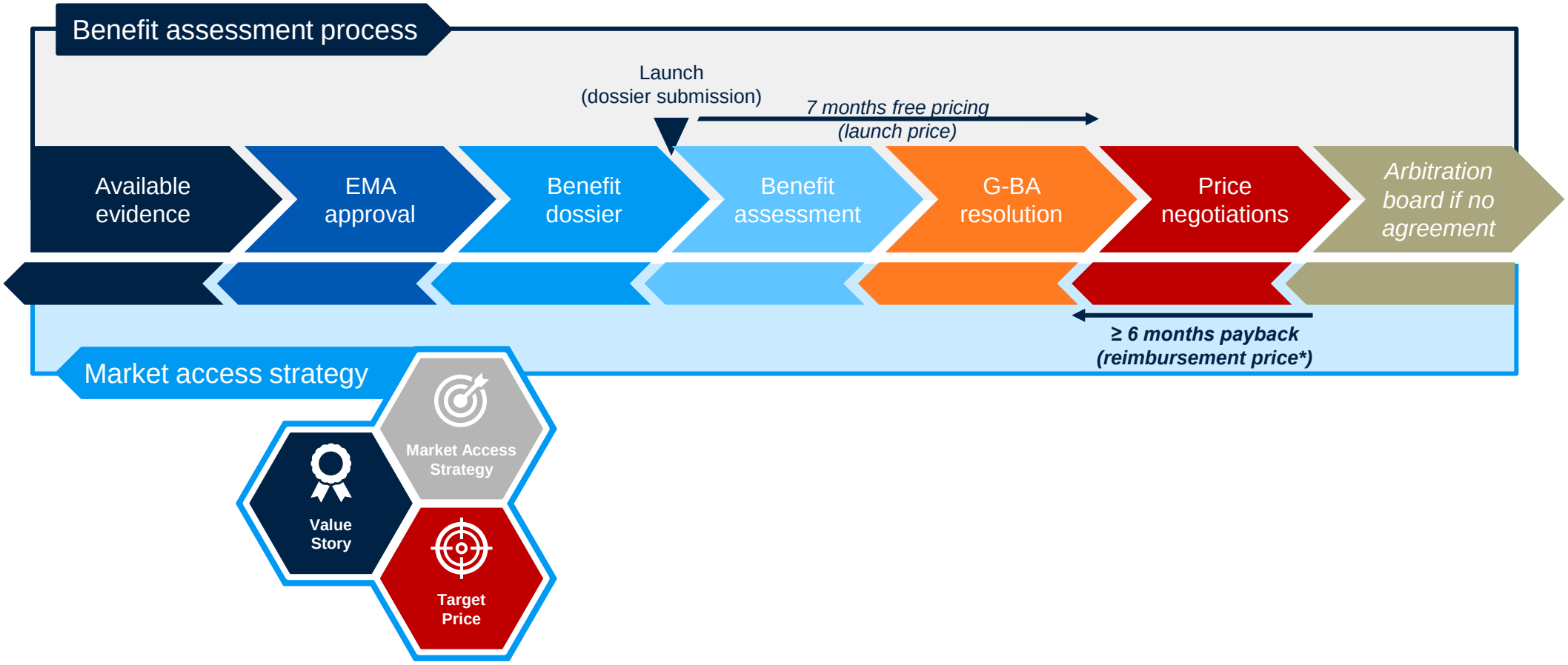
NEW THRESHOLD!
(≙ approx. € 23.8 million ex-factory price level)

As soon as revenues[1] from the pharmaceutical exceed € 30 million[2] over the past 12 months

Full assessment analogous to non-orphan drugs

[1]) 12 months' revenue based on pharmacy retail price (out-patient) and pharmacy retail price incl. VAT (in-patient), respectively (SGB V sect. 35a para. 1, cl. 12)
[2]) Formerly € 50 million, updated to € 30 million with GKV-FinStG end of 2022

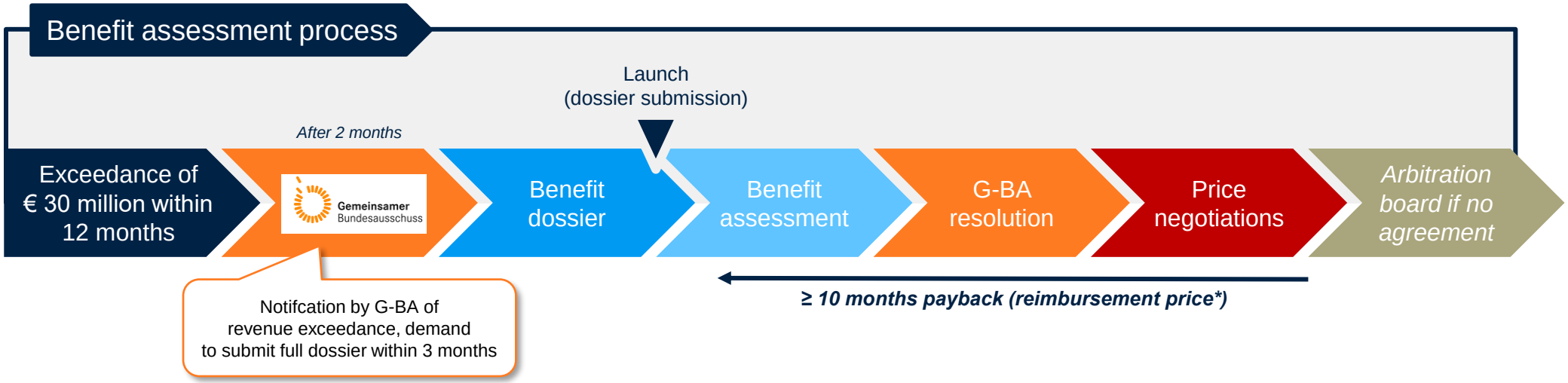
Reimbursement price will become effective retroactive as of month 7 after launch, leading to a longer payback period



*) effective from month 7; free pricing until month 7 after product launch; G-BA (Gemeinsamer Bundesausschuss): Federal Joint Committee

For orphan drugs exceeding the € 30 million revenue threshold, reimbursement price will become effective as of month 7 after exceedance…

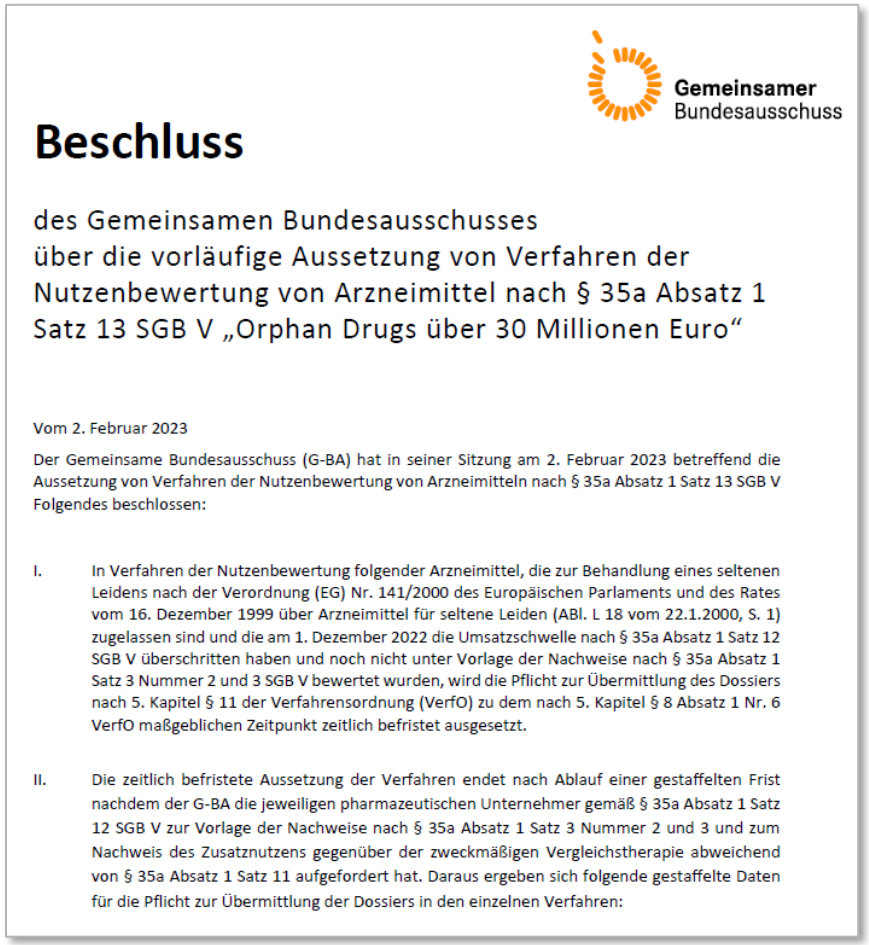
… i. e. during the benefit assessment and prior (!) to the price negotiations



*) effective from month 7 after date of revenue exceedance; G-BA (Gemeinsamer Bundesausschuss): Federal Joint Committee

9 orphan drugs exceeded the lower revenue threshold on December 1st 2022, but G-BA phased dossier submission to the 2nd half of 2023…

… while effective of date reimbursement price and payback period are scheduled for June 2023



Gemeinsamer Bundesausschuss

Beschluss

des Gemeinsamen Bundesausschusses
über die vorläufige Aussetzung von Verfahren der Nutzenbewertung von Arzneimittel nach § 35a Absatz 1 Satz 13 SGB V „Orphan Drugs über 30 Millionen Euro“

Vom 2. Februar 2023

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 2. Februar 2023 betreffend die Aussetzung von Verfahren der Nutzenbewertung von Arzneimitteln nach § 35a Absatz 1 Satz 13 SGB V Folgendes beschlossen:

I. In Verfahren der Nutzenbewertung folgender Arzneimittel, die zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden (ABl. L 18 vom 22.1.2000, S. 1) zugelassen sind und die am 1. Dezember 2022 die Umsatzschwelle nach § 35a Absatz 1 Satz 12 SGB V überschritten haben und noch nicht unter Vorlage der Nachweise nach § 35a Absatz 1 Satz 3 Nummer 2 und 3 SGB V bewertet wurden, wird die Pflicht zur Übermittlung des Dossiers nach 5. Kapitel § 11 der Verfahrensordnung (VerfO) zu dem nach 5. Kapitel § 8 Absatz 1 Nr. 6 VerfO maßgeblichen Zeitpunkt zeitlich befristet ausgesetzt.

II. Die zeitlich befristete Aussetzung der Verfahren endet nach Ablauf einer gestaffelten Frist nachdem der G-BA die jeweiligen pharmazeutischen Unternehmer gemäß § 35a Absatz 1 Satz 12 SGB V zur Vorlage der Nachweise nach § 35a Absatz 1 Satz 3 Nummer 2 und 3 und zum Nachweis des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie abweichend von § 35a Absatz 1 Satz 11 aufgefordert hat. Daraus ergeben sich folgende gestaffelte Daten für die Pflicht zur Übermittlung der Dossiers in den einzelnen Verfahren:

Effective date of reimbursement price and start of payback period at June 1st, 2023

Brand name / drug	Date for dossier submission and start benefit re-assessment
Yescarta® (Axicabtagen Ciloleucel)	July 1st, 2023
Alprolix® (Eftrenonacog alfa)	August 1st, 2023
Galafold® (Migalastat)	August 15th, 2023
Voxzogo® (Vosoritid)	September 1st, 2023
Reblozyl® (Luspatercept)	October 16th, 2023
Rydapt® (Midostaurin)	November 15th, 2023
Onpattro® (Patisiran)	December 1st, 2023
Prevymis® (Letermovir)	December 15th, 2023
Polivy® (Polatuzumab vedotin)	Januar 2nd, 2024

Source: https://www.g-ba.de/beschluesse/5867/ (last access: March 10, 2023)

Outlook: still some open questions – it remains exciting

New guard rails

Application of new guard rails to appropriate comparator “patient individual therapy”, “optimized standard therapy” or “therapy according to doctor's instructions” is still unclear

Recommended position: guard rails **are not applicable** to these appropriate comparators

Combination discount

Specimen agreement for the technical implementation of combination discount expected for March 2nd, 2023 for identification of prescriptions of combination therapies

“Waste discount”

Correlation between waste and “waste discount” not specified, currently no precedents

Can GKV-SV prove that application of medicinal product leads to waste?

Agenda

1 Intro: Overview P&R-Process in Germany

2 New Law: Pricing implications of GKV-FinStG

3 "The Earthquake": Court Decision by BSG

Short disclaimer

- I am a health economist providing strategic and tactic advice, not a lawyer (but Alexander is ;)).
- This presentation is not intended to constitute legal advice, but to make you aware of questions which should be discussed with competent experts.
- If you need legal support, please consult a lawyer competent in this topic (AMNOG, §§ 35a, 130b SGB V).

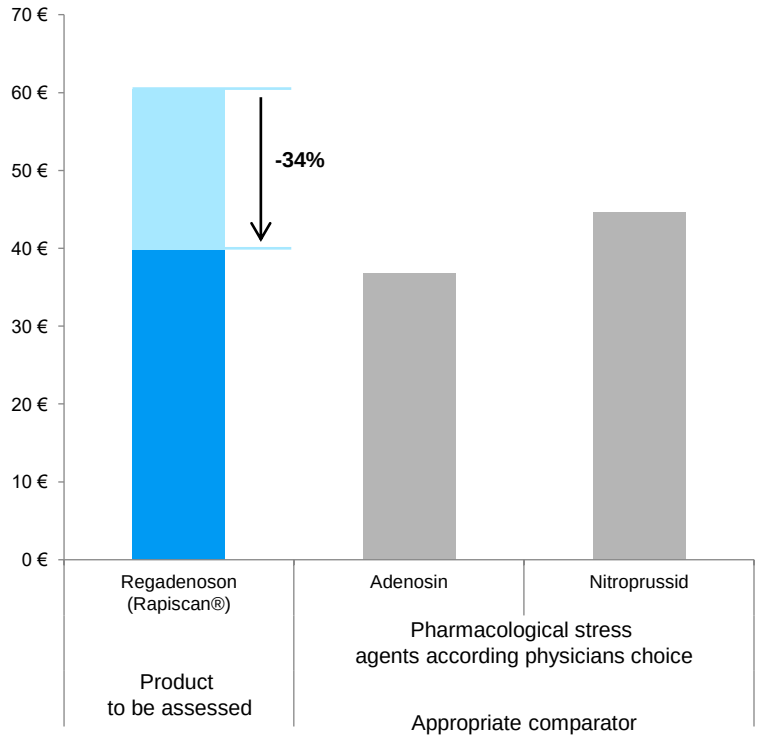
Regadenoson for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography (2nd indication, 2019)

Benefit Assessment

- No slicing
- App. comparator: Pharmacological stress agents according physicians choice
- Additional benefit not proved (no dossier submitted)
- Reimbursement price set by arbitration board

Outcome price negotiation

Treatment cost [1] per patient



Reimbursed price

Pack, 400 µg, 1x5 ml[2]

List price launch[3]:	69,90 €
List price after 1st price negotiation:	54,00 €
Rebate: (38% on list price after 1st negotiation)	-20,64 €
Reimbursed price after 2nd negotiation:	**33,36 €**
Mandatory rebate: (0% on reimbursed price)	-0,00 €
Cost to GKV SV: (reimbursed price ./. Mandatory rebate)	33,36 €

► Total rebate: 52% (on list price launch)

[1] According G-BA resolution (AVP abzgl. Apotheken- und Zwangsabschläge (§ 130 u. 130a SGB V), zzgl. zusätzliche GKV-Leistungen)
[2] Largest SKU, all prices as ApU
[3] Sales channel from 15.12.2018 only via hospital pharmacies
Prices shown according to arbitration board decision (as of: 06.07.2020)

Arbitration board made a straight forward decision on July 1st, 2020

Key points

Arbitration board has to decide on reimbursement price, once there is a G-BA resolution

- Prior assessment as part of a method does not preclude benefit assessment as this is addressed in the resolution
- Assessing if request to submit a dossier was valid is out of scope for arbitration board

Even though G-BA classified adenosine and nitroprusside only as “comparators” (not “appropriate comparators”) for this assessment, they still define the price line for regadenoson

The reimbursement price is the maximum price for Germany, regardless how the product is sold, i.e. also in the case of direct sales to physicians (*Direktvertrieb*) or hospital distribution only.

What has the Federal Social Court stated on Feb 22nd, 2023?

1. Nature of the early benefit assessment is an assessment vs. the appropriate comparator.
2. If there is no appropriate comparator available, such an assessment is not according to law.
3. Once a new product is a “therapeutic soloist” (*therapeutischer Solist*), this is the case. Therapeutic soloist is given if there is no other pharmaceutical product approved for this indication and a non-pharmaceutical intervention is not a relevant alternative.
4. In that situation G-BA is not allowed to decide on additional benefit.
5. Hence the G-BA resolution is invalid. And an invalid resolution can not be the basis for an arbitration board.

So far the Federal Social Court (BSG) has published only a summary of the court meeting, including the decision and key reasons therefore (*Terminbericht*). The full verdict has to be published within the next months.

BSG: “*Über eine Zusatznutzenbewertung ist danach nicht zu beschließen, wenn eine zweckmäßige Vergleichstherapie nicht bestimmt werden kann, weil es sich bei dem Arzneimittel um einen (therapeutischen) Solisten handelt; ein begonnenes Nutzenbewertungsverfahren ist dann zu beenden. Ist für ein Anwendungsgebiet nur ein Arzneimittel zugelassen und kommt als Vergleichstherapie nur eine medikamentöse Therapie in Betracht, kann der zulassungsüberschreitende Einsatz anderer Arzneimittel im sogenannten Off-Label-Use grundsätzlich ebenso nicht als zweckmäßige Vergleichstherapie gegenüber einem Arzneimittel mit - zulassungsrechtlicher - Solistenstellung angesehen werden.*“
Link: (https://www.bsg.bund.de/SharedDocs/Downloads/DE/Terminberichte/2023/2023_04_Terminbericht.pdf?__blob=publicationFile&v=2

What are the take aways of the BSG decision so far?

Background

- The Federal Social Court (*BSG*) defines how the current law has to be interpreted.
- The law might change, but changes will be effective only in and for the future
- Key for the BSG is that a benefit assessment vs a not approved treatment is invalid. Such a soloist must not be assessed.
- So far only the summary (*Terminbericht*) has been published, not the actual verdict. Note that the actual verdict might be more restricted in some statements (even thought it is difficult to see how this can be done).

For discussion

- What about prices set by the arbitration board for such soloists: Are they invalid automatically – or is there need for action for the company?
- What about prices negotiated freely for such soloists: Are they invalid automatically – or is there need for action for the company?
- And what about products which referred to soloists in the price negotiation?
- If and how invalid price discounts will be compensated?
- Will G-BA repel invalid resolutions automatically – or is there a need for action for the company?
- What is such a therapeutic soloist? Off label is clear. But what about BSC, physicians choice, watchful waiting? What about orphan drugs in general? What about PUMA, CUP, etc.?
- What about sales thresholds (1 Mio €, 50 / 30 Mio €)?

Three situations might be of particular relevance

A. Soloist according to BSG (only off-label as appropriate comparator)

- *Terminbericht* makes a clear, general statement on this situation
- Will it be reflected in final ruling?
- What about reimburseable off-label products (*Anlage VI)*? But is there a legal basis for *Anlage VI*, once there is an approved product in this indication?

B. Likely / potential sololist

- Orphan medicinal product → sololist per se?
- PUMA → sololist per se?:
- BSC as comparator → sololist per se?
- Patient individual therapy as comparator → sololist per se?
- Compassionate use program (CUP) → sololist per se?
- Direct import (§73 III AMG) → sololist per se?
- Watchful waiting (WW) → sololist per se?

C. (Likely / potential) sololist in price negotiation

- Appropriate comparator of the new product is (or could be) sololist: One could argue that the negotiated price of the sololist is unlawful and has to be replaced by launch price
  - But GKV-SV could counter by saying that so far the company selling the presumed sololist has not shown any intention to raise prices.
- Comparable pharmaceutical in the price negotiation is (or could be) sololist: see above

Note: Implication of „reimburseable off label products unclear“

Potential implications for AMNOG-Process

Preliminary ideas – no experience so far

	A. Soloist according to BSG (only off-label as appropriate comparator)	B. Likely / potential sololist	C. (Likely / potential) sololist in price negotiation
Advice meeting	• Ask for confirmation that product is not subject to AMNOG • Add “with reservation” (*unter Vorbehalt*) in notes	• Argue in advice meeting if (and why) situation is similar to BSG decision • Add reservation in notes (if appropriate)	• Ask for confirmation that price of sololist comparator is to be presented as initial price (as if no AMNOG)
Dossier prep.	• Submit dossier “with reservation”	• Submit dossier “with reservation” • § 73 III AMG / CUP as potential inroads	• Adjust cost presentation in section 3.4 of dossier to price of this product if sololist status would have been accepted
Hearing	• Participate “with reservation” • Ask trade organisations for confirmatory statements in hearing	• Participate “with reservation” • Ask trade organisations for confirmatory statements in hearing	• n/a
Price negotiation	• Participate “with reservation” or forward directly to arbitration board	• Participate “with reservation” or forward directly to arbitration board	• Confront GKV-SV with cost presentation in section 3.4 • Proceed in price negotiation “with reservation” in case GKV-SV does not accept
Further aspects	• Demand annulment of resolution by G-BA / price agreement by GKV-SV (?)	• Demand annulment of resolution by G-BA / price agreement by GKV-SV (?)	• Demand annulment of resolution by G-BA / price agreement by GKV-SV (?)

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Thanks for your attention!

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