# Do market withdrawals impact patient access to treatment in Germany?

AK Pownell, PRMA Consulting Ltd, Fleet, UK

## Introduction

- Under the AMNOG legislation introduced in 2011, the G-BA determines the extent and certainty of additional benefit (AB) of new therapies relative to the appropriate comparator therapy (ACT) through its early benefit assessment.
- For products that are found to have no AB, or for which the AB could not be sufficiently demonstrated, annual therapy costs cannot exceed those of the ACT, even if this is best supportive care or includes generics.
- After the AB assessment, drug prices are negotiated with the GKV-Spitzenverband. The AB rating is an important factor in price negotiations, but the size of the patient population, the comparator treatment costs, and the price of the treatment in reference countries are also considered.
- If both parties cannot agree on a price, one will be determined within 3 months through arbitration.
- However, in cases where manufacturers do not accept the negotiated price, they may stop distribution in Germany to protect the price in other markets.
- Therefore, we wanted to understand the number and timing of withdrawals and their impact on supply to patients.

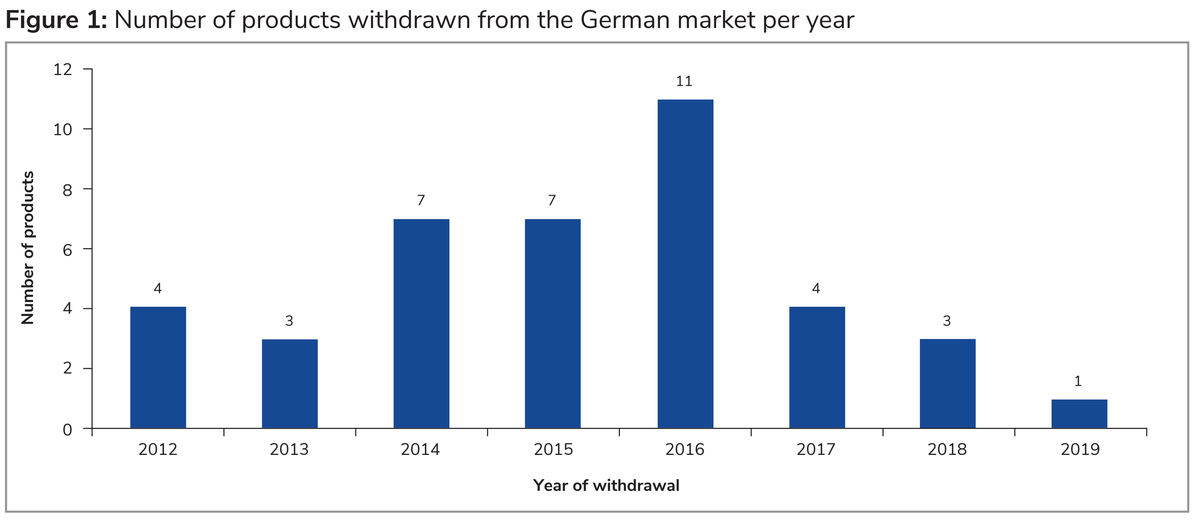
## Methods

- We analyzed all G-BA assessments[1] conducted before 13 May 2019 for products that were withdrawn.
- The current sales status on Lauer Taxe[2] was reviewed on 15 May 2019. If a product was no longer listed on Lauer Taxe, it was assumed to have been withdrawn.
- The reasons for withdrawal were identified from the GKV-Spitzenverband status[3] and additional publications.[4,5]

## Results

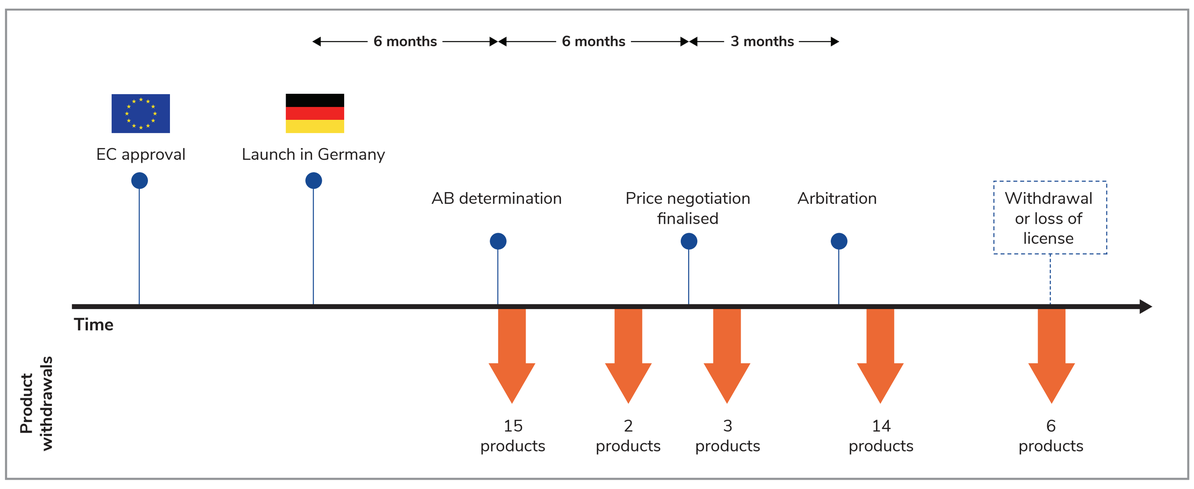
- We identified 40 products that had been withdrawn from the German market since 2011 (Figure 1).

**Figure 1:** Number of products withdrawn from the German market per year




- Across the 40 product withdrawals, 15 were within 4 weeks of the AB determination (opt-out), and 2 during price negotiations (Figure 2). Opting out at this point prevents publication of a negotiated price that could be referenced by other countries.
- A further 3 products were withdrawn after price negotiations; 14 were withdrawn after a price was determined through arbitration.
- In addition, 6 products are no longer available because their license was withdrawn or had expired.

**Figure 2:** Time point of product withdrawals




- Across all 40 products, the G-BA assigned no AB for any subgroup to 29 products (72%).

**Figure 3:** Highest level of AB assigned to at least one subgroup

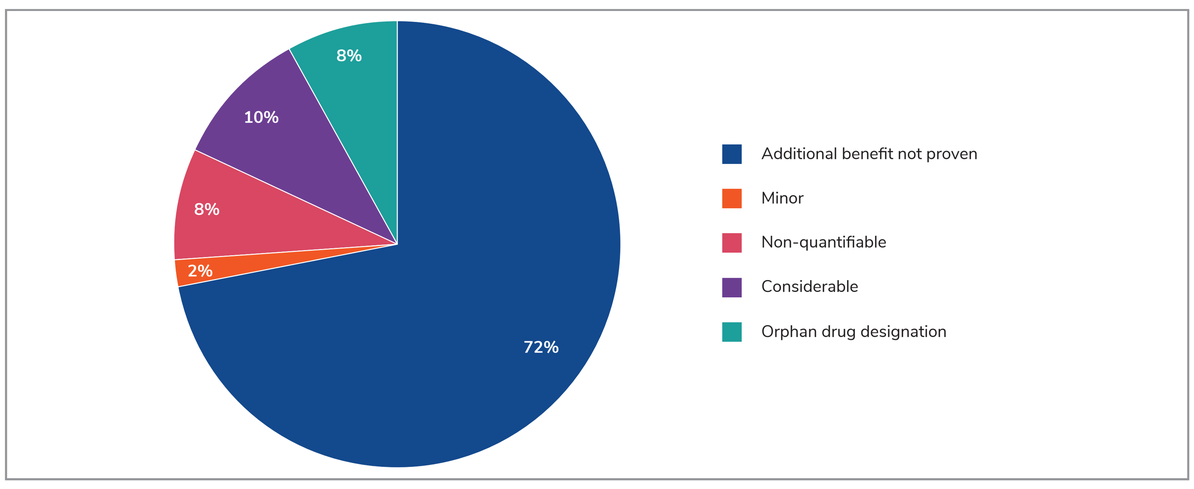



**Table 1:** Details of identified product withdrawals

| Active substance (brand name, manufacturer) | Indication | G-BA resolution | Year | Current status | Conditions for re-introduction |
|---|---|---|---|---|---|
| Within 4 weeks of AB determination (opt-out) | | | | | |
| Aliskiren + amlodipine (Rasilamlo®, Novartis) | Essential hypertension | AB not proven | 2012 | Distribution stopped | – |
| Bosutinib (Bosulif®, Pfizer) | Chronic myeloid leukemia | ODD; extent: non-quantifiable | 2013 | Available | Re-introduced after price re-negotiations |
| Brivaracetam (Briviact®, UCB) | Epilepsy | AB not proven | 2016 | Available | Re-introduced after price re-negotiations |
| Canagliflozin (Invokana®, Janssen-Cilag) | Diabetes mellitus type 2 | AB not proven | 2014 | Distribution stopped | – |
| Canagliflozin + metformin (Vokanamet®, Janssen-Cilag) | Diabetes mellitus type 2 | AB not proven | 2015 | Distribution stopped | – |
| Collagenase Clostridium histolyticum (Xiapex®, Pfizer) | Dupuytren's contracture | AB not proven | 2012 | Distribution stopped | – |
| Empagliflozin + metformin (Synjardy®, Boehringer Ingelheim) | Diabetes mellitus type 2 | AB not proven | 2016 | Distribution stopped | – |
| Gaxilose (LacTest®, Venter) | Hypolactasia | AB not proven | 2016 | Distribution stopped | – |
| Lomitapide (Lojuxta®, Aegerion) | Hypercholesterolemia | AB not proven | 2014 | Distribution stopped | – |
| Lurasidone (Latuda®, Takeda) | Schizophrenia | AB not proven | 2015 | Distribution stopped | – |
| Osimertinib (Tagrisso®, AstraZeneca) | Non-small cell lung cancer | AB not proven | 2016 | Available | Single import, re-introduced after re-assessment, new study data |
| Ospemifene (Senshio®, Shionogi) | Post-menopause | AB not proven | 2017 | Distribution stopped | – |
| Pitavastatin (Livazo®, Merckle Recordati) | Hypercholesterolemia; dyslipidemia | AB not proven | 2013 | Available | Hospital setting, re-introduced after price determination |
| Retigabine (Trobalt®, GSK) | Epilepsy | AB not proven | 2012 | Distribution stopped | Single import, but distribution stopped world-wide since |
| Tafluprost + timolol (Taptiqom®, Santen) | Glaucoma, ocular hypertension | AB not proven | 2015 | Available | Re-introduced after price re-negotiations |
| During price negotiation | | | | | |
| Insulin glargin + lixisenatide (Suliqua®, Sanofi) | Diabetes mellitus type 2 | AB not proven | 2018 | Distribution stopped | – |
| Linagliptin (Trajenta®, Boehringer Ingelheim) | Diabetes mellitus type 2 | AB not proven | 2012 | Distribution stopped | – |
| After price negotiation | | | | | |
| Dasabuvir (Exviera®, AbbVie) | Hepatitis C | Indication of considerable AB for 2 subgroups; hint of considerable AB for 2 subgroups; hint of minor AB for 6 subgroups | 2017 | Distribution stopped | – |
| Ombitasvir + paritaprevir + ritonavir (Viekirax®, AbbVie) | Hepatitis C | Indication of considerable AB for 2 subgroups; hint of considerable AB for 2 subgroups; hint of minor AB for 8 subgroups; AB not proven for 2 subgroups | 2017 | Distribution stopped | – |
| Regorafenib (Stivarga®, Bayer) | Colorectal cancer/GIST | AB not proven | 2016 | Distribution stopped | – |
| After arbitration | | | | | |
| Albiglutide (Eperzan®, GSK) | Diabetes mellitus type 2 | Hint of minor AB for 1 subgroup; AB not proven for 3 subgroups | 2018 | Distribution stopped | – |
| Ataluren (Translarna®, PTC Therapeutics) | Duchenne muscular dystrophy | ODD; extent: minor AB | 2016 | Distribution stopped | – |
| Bromfenac (Yellox®, Bausch & Lomb) | Inflammation of the eye | AB not proven | 2014 | Distribution stopped | – |
| Daclatasvir (Daklinza®, BMS) | Hepatitis C | Hint of minor AB for 1 subgroup; hint of considerable AB for 1 subgroup; AB not proven for 5 subgroups | 2019 | Distribution stopped | – |
| Insulin degludec (Tresiba®, Novo Nordisk) | Diabetes mellitus type 1 and 2 | AB not proven | 2016 | Available | Re-assessment, new study data |
| Insulin degludec + liraglutide (Xultophy®, Novo Nordisk) | Diabetes mellitus type 2 | AB not proven | 2016 | Distribution stopped | – |
| Linaclotide (Constella®, Almirall) | Irritable bowel syndrome with constipation | AB not proven | 2014 | Available | Hospital setting, re-introduced after price re-negotiations |
| Living larvae of *Lucilia sericata* (BioBag®, BioMonde) | Wound healing | AB not proven | 2015 | Available | Hospital setting, re-introduced after price re-negotiations |
| Lixisenatide (Lyxumia®, Sanofi) | Diabetes mellitus type 2 | AB not proven | 2014 | Distribution stopped | – |
| Mirabegron (Betmiga®, Astellas) | Hyperactive bladder | AB not proven | 2015 | Available | Re-introduced after price re-negotiations |
| Perampanel (Fycompa®, Eisai) | Epilepsy | AB not proven | 2013 | Available | Manufacturer-sponsored import program, re-introduced after price re-negotiations |
| Vildagliptin (Galvus®, Jalra®, Xiliarx®, Novartis) | Diabetes mellitus type 2 | AB not proven | 2014 | Available | Re-introduced after price re-negotiations |
| Vildagliptin + metformin (Eucreas®, Icandra®, Zomarist®, Novartis) | Diabetes mellitus type 2 | AB not proven | 2014 | Available | Re-introduced after price re-negotiations |
| Vortioxetin (Brintellix®, Lundbeck) | Depression | AB not proven | 2016 | Distribution stopped | – |
| After arbitration | | | | | |
| Alipogene tiparvovec (Glybera®, Chiesi) | Hyerlipoproteinemia type 1 | ODD; extent: non-quantifiable | 2017 | Distribution stopped | – |
| Boceprevir (Victrelis®, MSD Sharp & Dome) | Hepatitis C | Indication of non-quantifiable AB | 2016 | Distribution stopped | – |
| Colestilan (BindRen®, Mitsubishi) | Hyperphosphataemia | AB not proven | 2015 | Distribution stopped | – |
| Simeprevir (Olysio®, Janssen-Cilag) | Hepatitis C | Hint of minor AB for 2 subgroups; Indication of considerable AB for 3 subgroups; AB not proven for 2 subgroups | 2018 | Distribution stopped | – |
| Sipuleucel-T (Provenge®, Dendreon) | Prostate cancer | Hint of non-quantifiable AB | 2015 | Distribution stopped | – |
| Telaprevir (Incivo®, Janssen-Cilag) | Hepatitis C | Indication of non-quantifiable AB | 2016 | Distribution stopped | – |

AB, additional benefit; G-BA, Gemeinsamer Bundesausschuss (Federal Joint Committee); GIST, gastrointestinal stromal tumor; ODD, orphan drug designation

- However, access to the withdrawn products was continued in some cases.
  - For 3 products, the supply was continued through pre-approved imports covered by the statutory health insurance (SHI) funds (retigabine, osimertinib) or through manufacturer-sponsored imports (perampanel).
  - Because the early benefit assessment was applicable to outpatient products only (until 2019), a further 3 products (living larvae of *Lucilia sericata*, linaclotide, and pitavastatin) were withdrawn only from the ambulatory sector, and supply was continued for inpatients.
- Overall, 12 of the 40 withdrawn products were subsequently re-introduced and are available in the outpatient and inpatient settings.
  - In 8 cases, a price was agreed after the withdrawal, and the product was re-introduced.
  - For 2 products (insulin degludec, osimertinib), the manufacturer initiated a re-assessment with new data. Although for insulin degludec the re-assessment still resulted in no AB, the manufacturer did not withdraw the product a second time.

## Conclusions

- Product withdrawals restrict access and lead to treatment disruption for patients.
- Several pathways exist for continuing supply to German patients; however, treatment disruptions due to delayed price agreements or re-introductions are still likely.
- While statutory health insurance funds argue that withdrawals from the market following a resolution of no AB do not affect patients, since therapies with the same efficacy are available, 27% of the identified withdrawals were for products with an assigned an AB for at least one subgroup.
- In addition, no AB is often assigned for purely methodological reasons, such as lack of comparative studies with the ACT.
- Therefore, further research is warranted on the impact of withdrawals and treatment switching on patients.

## Limitations

- Using this methodology, we are unable to quantify the number of patients affected or the extent of the impact.
- This study is based on publicly available information only, and the expected price reductions discussed in confidential price negotiations cannot be assessed.


### References

1. G-BA: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/
2. Lauer Taxe: https://webapo-info.lauer-fischer.de/LTO40.160101/taxe
3. GKV-Spitzenverband: https://www.gkv-spitzenverband.de/krankenversicherung/arzneimittel/verhandlungen_nach_amnog/ebv_130b/ebv_nach_130b.jsp
4. BPI: AMNOG Daten, 2017; AMNOG Daten, 2018; and AMNOG Daten, 2019
5. Arzneimittel-Atlas, 2018



### Acknowledgments

This work was conducted and funded by PRMA Consulting.

The author would like to acknowledge Clare Jones, who contributed to the conceptualization of this work and provided review comments.