German early benefit assessments of orphan drugs under full dossier conditions

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Objectives

Market access in Germany provides several advantages for orphan drugs in the course of the early benefit assessment, since the additional benefit is already granted by law on the basis of the marketing authorization and its substantiating studies. However, this no longer applies if the drug's turnovers has exceeded 50 million Euro over the past 12 months leading to additional requirements along the benefit assessment (full dossier requirements). In this case, the additional benefit is not legally assured and must be demonstrated in comparison to the corresponding appropriate comparative therapy and taking a higher level of evidence into account.

The objective is to analyze the already completed procedures regarding their underlying evidence and the additional benefit granted by IQWiG and G-BA as well as the impact on the subsequent price negotiations.

Methods

All published documents of the early benefit assessments of those orphan drugs whose turnovers have exceeded the 50 million Euro threshold over the past 12 months until July 2018 were analyzed in terms of:

- available evidence,
- appropriate comparative therapy,
- G-BA methodology, and
- negotiated prices.

A total of six procedures were analyzed:

- Ruxolitinib (Jakavi®)
- Pomalidomid (Imnovid®)
- Ibrutinib (Imbruvica®)
- Macitentan (Opsumit®)
- Daratumumab (Darzalex®)
- Carfilzomib (Kyprolis®)

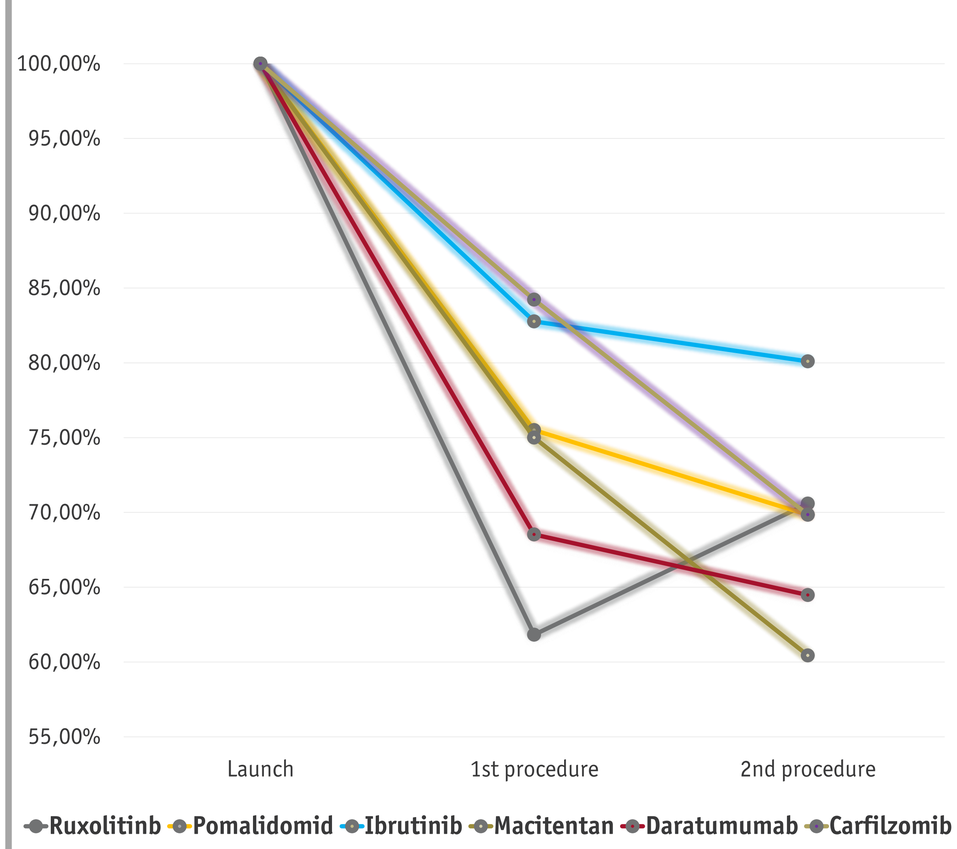
Results

Drug name, Manufacturer	1st procedure	2nd procedure after sales exceeded 50 million	ACT fulfilled	Benefit change
Jakavi® (Ruxolitinib), Novartis	blinded RCT, Phase III, ongoing comparator: placebo **MINOR**	later data cut off **CONSIDERABLE**	✓	↑
Imnovid ® (Pomalidomid), Celgene	open RCT, Phase III, ongoing comparator: high dose dexamethasone **CONSIDERABLE**	later data cut off Subpopulation a: **CONSIDERABLE** Subpopulation b: **NO BENEFIT**	✓ ✗	→ ↓
Imbruvica ® (Ibrutinib), Janssen-Cilag	Field of application 1: single-arm, open Phase II study comparator: n/a **NON-QUANTIFIABLE**	Field of application 1: open RCT, Phase III comparator: temsirolimus a) **CONSIDERABLE** b) **NO BENEFIT**	✓ ✗	↑ ↓
	Field of application 2: open RCT, Phase III comparator: ofatumumab a) **NON-QUANTIFIABLE** b) **NON-QUANTIFIABLE**	Field of application 2: no changes to 1st assessment comparator: ofatumumab a) **NO BENEFIT** b) **NON-QUANTIFIABLE** c) **NON-QUANTIFIABLE**	✗ ✓ ✓	↓ → →
Opsumit ® (Macitentan), Actelion Pharmaceuticals	blinded RCT, Phase III comparator: placebo **MINOR**	no evidence versus ACT **NO BENEFIT**	✗	↓
Darzalex ® (Daratumumab), Janssen-Cilag	single-arm, open Phase II-study comparator: placebo **NON-QUANTIFIABLE**	no evidence versus ACT **NO BENEFIT**	✗	↓
Kyprolis ® (Carfilzomib), Amgen	Field of application 1: open Phase III-RCT, ongoing comparator: Lenalidomid plus Dexamethason **NON-QUANTIFIABLE**	Field of application 1: later data cut **CONSIDERABLE**	✓	↑
	Field of application 2: open Phase III-RCT, ongoing comparator: : bortezomib plus dexamethason **MINOR**	Field of application 2: later data cut **CONSIDERABLE**	✓	↑

Evidence

- All but one oncology drug were able to confirm the previously granted additional benefit, the cardiological one failed to prove the additional benefit compared to a patient-individually optimized drug therapy according to the physician's requirements.
- Two procedures were be able to prove a higher benefit category within the second procedure versus the appropriate comparative therapy; both already had RCTs in the 1st procedure and met the ACT defined by the G-BA.
- For two procedures, the G-BA sliced the population and differentiated the additional benefit between the defined subpopulation.
- If the 50 million Euro threshold is exceeded, the requirements for a full dossier apply, which is why the decision in case the ACT is not fulfilled is "no additional benefit" (no exemption).
- In most of the procedures a considerable additional benefit was based on prolonging OS.

Figure 1: Negotiated rebates for orphan drugs per highest benefit category



Rebate (net)

Ruxolitinb
1st procedure 38.18%
2nd procedure 29.41% ↑

Pomalidomid*
1st procedure 24.50%
2nd procedure 30.16% ↓

Ibrutinib
1st procedure 17.23%
2nd procedure 19.90% ↓

Macitentan
1st procedure 25.00%
2nd procedure 42.89% ↓

Daratumumab
1st procedure 31.48%
2nd procedure 35.52% ↓

Carfilzomib
1st procedure 15.78% (30.34%)**
2nd procedure 30.15% ↓

* Based on Package: 4mg, 21 Pieces (PZN: 10022793); **combination therapy with lenalidomid and dexamethasone

Impact on price negotiations

- Rebates were negotiated between 15.78% and 38.18% in the 1st procedures and 19.90% and 42.89% in the 2nd procedures.
- Only one product was able to achieve a lower rebate after the second price negotiation compared to the first procedure (i.e. a de facto price increase). This was possible because, in contrast to the first process (minor additional benefit), the G-BA confirmed a considerable additional benefit for ruxolitinb.
- The highest rebate was negotiated for macitentan with an additional rebate of +17.89% compared to the first negotiation as there was no evidence available which could prove an additional benefit versus the ACT.
- In two cases the rebate was arbitrated. An arbitration is the only option, if negotiations between the two parties (GKV-SV and pharmaceutical manufacturer) do not come to a solution within four to five rounds:
  - 1st procedure daratumumab (31,48%)
  - 1st procedure pomalidomid (24,50%*)

Conclusion

So far, sales of only 6 orphan drugs exceeded the 50 million Euro threshold. Analyzed precedents show an overbalance on the side of oncology drugs (5 oncology products, 1 cardiological drug). Besides the high annual therapy costs of theses drugs, the overweight is also triggered by label extensions in the case of these oncological products.

Analyses could demonstrate that the underlying evidence and the ACT defined by the G-BA play a decisive role when an orphan drug is reassessed after exceeding the 50 million Euro threshold, as the more formal assessment of early benefit under full dossier conditions does not take into account the orphan drug status. However, it could also be shown that especially the pharmaceuticals for the treatment of rare cancers are more able to confirm the additional benefit because their studies more often comply with real care situations in terms of the applied therapy option and the evaluated endpoints. The only non-oncological drug macitentan failed to prove the previously granted additional benefit compared to a patient-individually optimized drug therapy according to the physician's requirements. The subsequently negotiated rebate demonstrates the major challenges of a reassessment under non-orphan dossier conditions. To what extent this also applies to other non-oncologicals remains to be seen. Therefore, it is necessary to await further reassessments of rare and high-priced drugs outside oncology to be able to draw further conclusions.

Nevertheless, it makes sense to develop the launch strategy for orphan drugs in view of the expected label extensions and sales expectations, especially with regard to oncologics and other high-priced drugs for the treatment of rare diseases.

ACT: appropriate comparative therapy; add. benefit: additional benefit; BSC: best supportive care; G-BA: Federal Joint Committee; GKV-SV: umbrella organization of the SHIs; OS: overall surival

References: 1 https://www.g-ba.de/informationen/nutzenbewertung/ | 2 https://www.cgm.com/lauer-fischer/index.de.jsp

schönermark
kielhorn
collegen

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PHP287 – Poster presented at ISPOR Europe 2018, 10-14 November 2018 in Barcelona, Spain