ASSESSING MEDICINAL PRODUCTS WITH LIMITED EVIDENCE IN GERMANY

Current experience

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BACKGROUND

For Orphan Drugs there are various special rules for benefit assessment in Germany, but not for other special regulatory situations. The following three special regulatory situations can be differentiated:

1. Conditional approval

… is given on the basis of less complete clinical data than is normally required, because it answers an unmet medical need. The applicant should be in a position to provide the comprehensive clinical data in the future. Conditional marketing authorisations are valid for one year, on a renewable basis.

2. Approval under exceptional circumstances

… is granted when the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use. Approval under exceptional circumstances is also valid for one year, on a renewable basis.

3. Paediatric-use marketing authorisation (PUMA)

… Paediatric-use marketing authorisation (PUMA) is a type of marketing authorisation covering the indication(s) and appropriate formulation(s) for the paediatric population, which was introduced by the Paediatric Regulation. The development of a PUMA must follow a paediatric investigation plan (PIP), to be agreed on by the Paediatric Committee (PDCO).

All special regulatory situations face the same challenge:

The regulatory authority has determined that existing evidence is limited and cannot be improved.

RESEARCH QUESTION

Do the IQWiG and the G-BA take into account that evidence might be limited in these special regulatory situations? And if so: how is it done?

METHODS

As of June 2015 EMA lists 25 medicinal products in special regulatory situations, which are not approved as Orphan Drugs:

- 10 products with a conditional approval,
- 13 products with an approval under exceptional circumstances,
- 2 products with paediatric-use marketing authorisation.

Out of 135 resolutions made by G-BA so far 7 resolutions are in special regulatory situations as described before.

All 7 assessments have been analysed in detail regarding their underlying evidence and how this evidence was evaluated by the IQWiG and the G-BA.

DISCUSSION

- By giving approval in special regulatory situations the EMA determines that evidence is limited.
- Regulatory approval is binding for benefit assessment. Hence limitations in study design which cause lower level evidence or limited number of endpoints have to be taken into account for benefit assessment.
- However: formal requirements (formal completeness, comparison against comparator as defined by the G-BA, statistical significance, etc.) still have to be followed.
- As a consequence dossiers have been rejected only for formal reasons, not for insufficient evidence.
- Limited duration:
  - Resolutions limited in duration are granted quite often as companies have to submit further data to the EMA (as a consequence of their special status)
  - The G-BA explicitly refers to special regulatory status when limiting duration
  - If there is no limitation, the G-BA does not provide reasons

CONCLUSION

- In these three special regulatory situations additional benefit is not guaranteed by law.
- However the G-BA is more flexible regarding which evidence is considered being sufficient.
- Reasons for limitations of duration (or their absence) are not always clear.
- Note that this analysis is based on 7 assessments only, so the informational value is limited and thus still limited in its predictive power.

RESULTS - IQWiG AND G-BA

1. Conditional approval

ACTIVE SUBSTANCE	EVIDENCE PRESENTED IN DOSSIER	ASSESSMENT BY IQWiG*	RESOLUTION BY G-BA*	LIMITED DURATION
Crizotinib *(Xalkori®)*	RCT	No additional benefit	Hint for considerable additional benefit	2 years
Vandetanib *(Caprelsa®)*	RCT	No additional benefit	Hint for minor additional benefit	3 years
Vismodegib *(Erivedge®)*	Case series	No additional benefit	Hint for minor additional benefit	2 years
Fampridin *(Fampyra®)*	RCT	No additional benefit	No additional benefit	No limitation
Pixantron *(Pixuvri®)*	RCT	No additional benefit	No additional benefit	No limitation

Additional benefit based on a prospective case series and „complete response“ as endpoint

„No additional benefit“ as evidence in dossier did not match to the comparator as defined by G-BA

2. Approval under exceptional circumstances

ACTIVE SUBSTANCE	EVIDENCE PRESENTED IN DOSSIER	ASSESSMENT BY IQWiG*	RESOLUTION BY G-BA*	LIMITED DURATION
Lomitapide *(Lojuxta®)*	Case series	No assessment by IQWiG	No additional benefit	1 year

No additional benefit as dossier was not complete

3. Paediatric-use marketing authorisation (PUMA)

ACTIVE SUBSTANCE	EVIDENCE PRESENTED IN DOSSIER	ASSESSMENT BY IQWiG*	RESOLUTION BY G-BA*	LIMITED DURATION
Propanolol *(Hemangiol®)*	RCT	Hint for major additional benefit	Hint for major additional benefit	No limitation

G-BA explicitly acknowledges existing hurdles

* Assessment refers to the subindication with the best result

REFERENCES

Special regulatory status can be searched via the EMA
(URL: www.ema.europa.eu > Find medicine > Human medicines)

Documents related to these 7 benefit assessments discussed here can be found under the G-BA
(URL: www.g-ba.de/informationen/nutzenbewertung)

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