EXTRAPOLATION IN GERMAN BENEFIT ASSESSMENT: THE CHALLENGING REQUIREMENTS FOR PEDIATRIC PHARMACEUTICALS

Rietzschel N, Ernst N, Pütz C

OBJECTIVES

The objective of the Pediatric Regulation (EC) No 1901/2006 is to ensure that medicines for use in children are of high quality, ethically researched and authorized appropriately. Its purpose is to achieve this without subjecting children to unnecessary trials. As RCT's are often difficult to perform in this age group, the European Medicines Agency (EMA) has introduced the concept of extrapolation from data of a source population, e.g., adults and adolescents, to the target population. The same holds true for HTA assessment in Germany in which such an extrapolation is also considered by law. In this poster we investigate if and how such an extrapolation is actually accepted by the Federal Joint Committee (G-BA) in benefit assessments.

METHODS

We screened all benefit assessments completed until September 15, 2019 with indication for a pediatric population (n = 65) and included all assessments in which the pharmaceutical company extrapolated data to claim additional benefit for the target population (n = 12). We analyzed the justifications to the resolution of G-BA and parts of the submitted dossier (module 4) to identify the necessary requirements for acceptance of data extrapolation.
All documents were taken from the G-BA website: www.g-ba.de/informationen/-nutzenbewertung/

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RESULTS

	Active ingredient (Trade name)	Indication	Assessed age group	Additional benefit of source population	Requirements			Extrapolation accepted by G-BA	Additional benefit of target population
					Medical need	Same comparator	EMA similarity		
PUMA	**Propranolol** (Hemangiol®)	Haemangioma	5 weeks – 5 months	Major	N/A	+	+	✓	Non-quantifiable
	Hydrocortisone (Alkindi®)	Adrenal insufficiency	0 – 18 years	(Only target population assessed)	+	-[1]	+	✗	Not proven
Oncology	**Vandetanib** (Caprelsa®)	Medullary thyroid carcinoma	5 – 18 years	Minor	+	+	+	✓	Non-quantifiable
	Ipilimumab (Yervoy®)	Melanoma	12 – 18 years	Considerable / not proven	-	-	-	✗	Not proven
	Blinatumomab (Blincyto®)	Acute lymphoblastic leukaemia	≥ 1 year	Considerable	+	OD[2]	-[3]	✗	Non-quantifiable
Infection	**Dolutegravir** (Tivicay®)	HIV-1 infection	6 – 12 years	Considerable / not proven	-	±	+	✗	Not proven
	Rilpivirin (Edurant®)	HIV-1 infection	12 – 18 years	Minor	-	+	+	✗	Not proven
	Ledipasvir/Sofosbuvir (Harvoni®)	Chronic hepatitis C	12 – 18 years	Considerable / not proven	+	±	+	✓	Non-quantifiable / not proven
	Sofosbuvir (Sovaldi®)	Chronic hepatitis C	12 – 18 years	Considerable / not proven	+	±	+	✓	Non-quantifiable
Other	**Teduglutide** (Revestive®)	Short bowel syndrome	1 – 18 years	Minor	+	OD[2]	+	✗	Non-quantifiable
	Mepolizumab (Nucala®)	Asthma	6 – 18 years	Minor / not proven	-	±	±[4]	✗	Not proven
	Lumacaftor/Ivacaftor (Orkambi®)	Cystic fibrosis	2 – 5 years	Considerable	+	+	+	✓	Non-quantifiable

[1] Comparing data between hydrocortisone (Alkindi®) and hydrocortisone (not Alkindi®) in adults would have been needed.
[2] For Orphan Drugs (OD) no comparison against appropriate comparative therapy is needed.
[3] EMA did not focus primarily on extrapolation for marketing authorization, G-BA sees uncertainties in similarity of target and source population.
[4] G-BA sees uncertainties in similarity of target and source population.
PUMA: Paediatric use marketing authorization.

- 10 of those 12 pharmaceuticals were first assessed for the adult (or adolescent) population and went through a second assessment when expanding the indication to a younger population.
- 2 of those 12 pharmaceuticals had a pediatric use marketing authorization (PUMA) and therefore used data extrapolation in their first assessment.
- In 5 of those 12 assessments data extrapolation was considered for benefit assessment by G-BA and an additional benefit against the appropriate comparative therapy was proven.
- In the majority of assessments the G-BA did not accept the extrapolation: Minor difference in disease manifestation or in the appropriate comparative therapy can lead to rejection by the G-BA. Not proven additional benefit for the source population automatically results in a non-proven additional benefit in the target population.
- A high unmet medical need can effect the outcome of benefit assessment positively: e.g., in chronic hepatitis C, extrapolation was accepted although the source population and the comparative therapy were partly not identical.
- So far, the best additional benefit granted based on extrapolation is non-quantifiable.

CONCLUSIONS

In order to maximize the probability of obtaining the acceptance of data extrapolation for early benefit assessment, all following requirements should be met:

- Granted additional benefit for the source population
- High unmet medical need
- Same appropriate comparative therapy for target and source population
- EMA confirmation of similarity of pharmacology (mode of action), disease manifestation and progression as well as clinical response (efficacy and safety)

Exceptions are indications in which the G-BA sees a high unmet medical need. For instance, in chronic hepatitis C, the requirements are not interpreted so strictly. In conclusion, G-BA reevaluates the similarity criteria although they have already been accepted for marketing authorization and in addition applies further criteria specific to German benefit assessments. The results lead to wonder whether pharmaceutical companies are able to fulfill the challenging requirements of the G-BA while complying with the Pediatric Regulation (EC) No 1901/2006.

Ecker + Ecker GmbH . Warburgstr. 50 . 20354 Hamburg . Germany
Phone: +49 (40) 41 330 81-0 . E-Mail: info@ecker-ecker.de . Internet: www.ecker-ecker.de