Orphan Drug Assessments in Germany in Comparison with Other International HTA Agencies

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Objective

- Examine benefit assessment of Orphan Drugs conducted by the German Federal Joint Committee (G-BA) according to AMNOG criteria, and compare them with assessments from five other national HTA agencies

Methods

- Analyzed all orphan drug assessments conducted by the G-BA between Jan 2011 and May 2015. Compared them with other HTA assessments from the EU (France, England, Netherlands, Scotland) and Canada. Data collection cut off was May 31, 2015
- 20 assessments for 19 Orphan Drugs were completed by the G-BA by end of May 2015 and were comparable with assessment of at least one other HTA agency
  - Ivacaftor was assessed twice by the G-BA, the first assessment being for the G551D mutation while the second one was for other 8 mutations
- Orphan Drug assessments were divided in three subgroups:
  - Ultra-orphan Drugs, i.e. drugs with both orphan drug designation(s) and approved indication(s) for conditions with prevalence of < 1:50,000 (as per NICE definition; 5 assessments);
  - Oncology Orphan Drugs i.e., all orphan drugs with both orphan drug designation(s) and approved indication(s) in oncology (9 assessments);
  - Other Orphan Drugs, i.e. orphan drugs not included in the previous two groups (6 assessments)
- All products and related assessments by the G-BA and other HTA agencies were also grouped in three categories – positive, partially positive and negative (Table 1) – to verify potential commonalities and/or differences in benefit evaluations and therefore in reimbursement and drug access
- Sources used for gathering information were websites of the following HTA authorities: Federal Joint Committee (G-BA, Germany); National Authority for Health (HAS, France); National Health Care Institute (ZIN, Netherlands); National Institute for Health and Care Excellence (NICE, England); Scottish Medicine Consortium (SMC, Scotland); Canadian Agency for Drugs and Technologies in Health (CADTH, Canada)

Table 1: Possible Outcomes and Ratings of HTAs conducted by the G-BA and other HTA Agencies

Germany (G-BA)	France (HAS)	Netherlands (ZIN)	England (NICE)	Scotland (SMC)	Canada (CADHT)
1 – Major additional clinical benefit	ASMR I Major Improvement of Medical Benefit	Inclusion on List 1B - Non-interchangeable drug with added therapeutic value	Recommended	Recommended	List
2 – Significant additional clinical benefit	ASMR II Important Improvement of Medical Benefit	Inclusion on List 1B with financial access arrangement		Recommended with Patient Access Scheme (PAS)	
3 – Marginal additional clinical benefit	ASMR III Moderate Improvement of Medical Benefit	Inclusion on List 1A - Interchangeable drug with equivalent therapeutic value	Recommended for restricted use	Recommended for restricted use	List with criteria and/or conditions (including price reduction)
4 – Additional clinical benefit not quantifiable	ASMR IV Minor Improvement of Medical Benefit		Recommended for restricted use with Patient Access Scheme (PAS)	Recommended for restricted use with Patient Access Scheme (PAS)	
5 – No additional clinical benefit	ASMR V No Improvement of Medical Benefit	Do not list	Not recommended	Not recommended	Do not list
6 – Lower additional clinical benefit			Not recommended (because of no submission)	Not recommended (because of no submission)	

Results

Table 2: Overall HTA decision summary by country / agency for all Orphan Drugs

HTA Agency	Completed Orphan Drug Evaluations	Positive Recommendations	Partially Positive Recommendations	Negative Recommendations	Assessment not completed / No assessment / Drug not marketed
Germany (G-BA)	20 (100%)	13 (65%)	7 (35%)	0 (0%)	0 (0%)
France (HAS)	20 (100%)	10 (50%)	7 (35%)	3 (15%)	0 (0%)
Netherlands (ZIN)	8 (40%)	5 (63%)	2 (25%)	1 (12%)	12 (60%)
England (NICE)	5 (25%)	0 (0%)	1 (20%)	4 (80%)	15 (75%)
Scotland (SMC)	14 (70%)	5 (35%)	4 (30%)	5 (35%)	6 (30%)
Canada (CADTH)	12 (60%)	1 (8%)	9 (75%)	2 (17%)	8 (40%)

Table 3: Summary of results for Ultra-orphan Drugs

HTA Agency	Completed Ultra Orphan Drug Evaluations	Positive Recommendations	Partially Positive Recommendations	Negative Recommendations	Assessment not completed / No assessment / Drug not marketed
Germany (G-BA)	5 (100%)	4 (80%)	1 (20%)	0 (0%)	0 (0%)
France (HAS)	5 (100%)	3 (60%)	0 (0%)	2 (40%)	0 (0%)
Netherlands (ZIN)	2 (40%)	0 (0%)	2 (100%)	0 (0%)	3 (60%)
England (NICE)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (100%)
Scotland (SMC)	2 (40%)	0 (0%)	2 (100%)	0 (0%)	3 (60%)
Canada (CADTH)	3 (60%)	0 (0%)	2 (67%)	1 (33%)	2 (40%)

Table 4: Summary of results for Oncology Orphan Drugs

HTA Agency	Completed Oncology Orphan Drug Evaluations	Positive Recommendations	Partially Positive Recommendations	Negative Recommendations	Assessment not completed / No assessment / Drug not marketed
Germany (G-BA)	9 (100%)	4 (44%)	5 (56%)	0 (0%)	0 (0%)
France (HAS)	9 (100%)	5 (56%)	3 (33%)	1 (11%)	0 (0%)
Netherlands (ZIN)*	1 (11%)	0 (0%)	0 (0%)	1 (100%)	8 (89%)
England (NICE)	4 (44%)	0 (0%)	0 (0%)	4 (100%)	5 (56%)
Scotland (SMC)	8 (89%)	5 (63%)	1 (12%)	2 (25%)	1 (11%)
Canada (CADTH)	5 (56%)	1 (20%)	4 (80%)	0 (0%)	4 (44%)

Table 5: Summary of results for Other Orphan Drugs

HTA Agency	Completed Other Orphan Drug Evaluations	Positive Recommendations	Partially Positive Recommendations	Negative Recommendations	Assessment not completed / No assessment / Drug not marketed
Germany (G-BA)	6 (100%)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
France (HAS)	6 (100%)	2 (33%)	4 (67%)	0 (0%)	0 (0%)
Netherlands (ZIN)	5 (83%)	5 (100%)	0 (0%)	0 (0%)	1 (17%)
England (NICE)	1 (17%)	0 (0%)	1 (100%)	0 (0%)	5 (83%)
Scotland (SMC)	4 (67%)	0 (0%)	1 (25%)	3 (75%)	2 (33%)
Canada (CADTH)	4 (67%)	0 (0%)	3 (75%)	1 (25%)	2 (33%)

- German G-BA and French HAS are the only agencies that reviewed all Orphan Drugs
- Other four HTA agencies completed between 14 and 5 evaluations, with these differences seemingly due to local criteria for reviews and / or launch timing; e.g.: NICE has not regularly reviewed ultra-orphan drugs; ZIN evaluates only outpatient drugs, therefore hospital oncology orphans are by definition not assessed
- German G-BA (65%), Dutch ZIN (63%) and French HAS (50%) have the highest percentages of positive recommendations without restrictions
- Canadian CADTH has the highest percentage (75%) of recommendations with clinical and economic restrictions
- England's NICE has the highest percentage (80%) of negative recommendations
- 43% of the Scottish SMC recommendations have a Patient Access Scheme and 36% took advice from a Patient and Clinician Engagement (PACE) group

Conclusions

- Germany did not issue any negative recommendations for any of the 20 Orphan Drug assessments
  - However, 7 assessments (35%) where the additional benefit was not quantifiable would have been negative if the products did not have an EMA Orphan Drug designation and a legislated «implicit additional clinical benefit»
  - Potential changes to the German drug assessment mechanism could impact this on definition and resulting evaluations
- Germany and France base their HTAs primarily on additional clinical value criteria, comparing the drug to existing treatment options, if any exist, or standard of care. As a consequence, there is substantial convergence in assessments, with only three cases having highly divergent assessments
- In England, Scotland and Canada, pharmacoeconomic criteria such as cost-effectiveness and cost-utility have a greater weight in the assessments
  - Stringent application of pharmacoeconomic criteria, such as cost-effectiveness and cost-utility, is associated with a significantly lower number of positive recommendations, especially in England (0%), Scotland (35%) and Canada (8%)
  - When comparing evaluation of Oncology Orphans in England and Scotland, there are significant discrepancies between the recommendations issued by the NICE and the SMC, with the latter issuing a higher number of positive recommendations, primarily as the result of greater importance attributed to the opinion of patients and clinicians (PACE groups)
- Providing evidence of low budget impact (Netherlands) and negotiating a price reduction or a Patient Access Scheme (Scotland, Canada) increases probability of positive or partially positive recommendation