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HETEROGENEITY IN RELATIVE EFFICACY ASSESSMENTS (REA) ACROSS EUROPEAN HTA BODIES: OPPORTUNITY FOR IMPROVING EFFICIENCY AND SPEED OF ACCESS TO PATIENTS?

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BACKGROUND

- Health Technology Assessment (HTA) agencies in Europe provide recommendations on medicines and other health interventions based on systematic clinical and/or economic evaluations which are conducted post marketing authorization by the European Medicines Agency (EMA).
- A robust economic evaluation will measure the monetary costs and benefits in the specific setting, relying on locally available data (e.g. the cost of alternative treatments or of medical services associated to the medicine being assessed). This naturally leads to some differences in the medical value of innovative treatments across the European Union (EU).
- Surprisingly, HTAs also reach different conclusions on the incremental therapeutic benefit of innovative medicines, although the data studied is predominantly the same for all markets (e.g. safety and efficacy data from RCTs). Although the underlying clinical data set is similar, HTAs diverge in their preference and interpretation of such data, e.g. in regards to trial design, relevant endpoints, appropriateness of defined patient subgroups or treatment comparators.
- The differences in the evaluation of a medicine's clinical parameters and of its added therapeutic benefit can potentially confuse stakeholders such as patients, physicians or pharmaceutical manufacturers.
- Heterogeneity in the appraisal of same clinical data also contributes to the divergence in reimbursement status and delays accessibility of novel drugs to patients in different EU member states.

OBJECTIVE

- The objective of this study was to identify differences in relative efficacy assessment (REA) by EU-HTA agencies, discuss the impact of this variation on time to patient access and assess the potential benefits of a harmonised REA as starting point for national HTAs.

METHODOLOGY

In order to understand the differences in HTA assessment, the following approach was adopted.

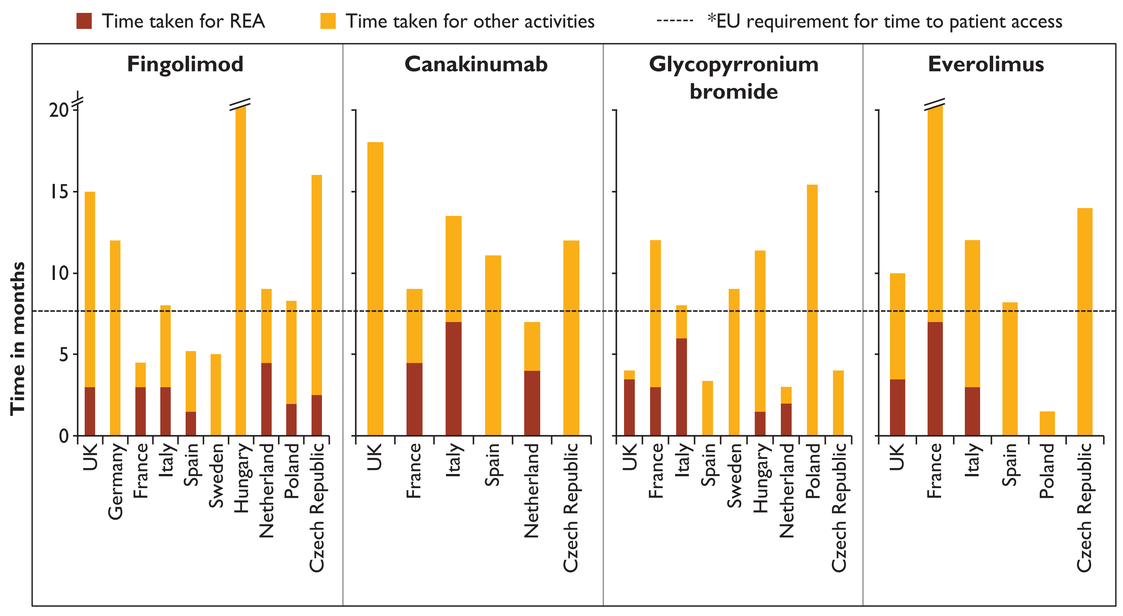
- In the first approach, four Novartis drugs from different therapeutic areas which had received EMA approval from 2009 onwards (fingolimod, canakinumab, everolimus and glycopyrronium bromide) were selected
  - HTA assessments were studied in 10 EU markets.
  - Structured Telephone interviews were conducted with Novartis Country Organisations in order to collect data on various parameters:
    - Time to clinical evaluation and patient access
    - Local HTA acceptance of clinical aspects
    - Rating of clinical relevance and differences between the EMA's regulatory label and local country reimbursement criteria
- In the second approach, we selected EMA approved non-Novartis drugs from the literature to see if similar findings resonated.
- Additionally, inputs from Novartis Country Organisations were collected on how HTA in their respective countries might be positively or negatively impacted, if a harmonized pan EU REA process existed.

RESULTS

Novartis drugs

- The average time taken by HTA agencies of EU member states to evaluate the clinical benefits and determine the added therapeutic benefit was 3 – 5 months. The total time to complete the HTA varied from 7.2 months to 12.3 months, which was longer than the EU requirement of 6 months for pricing and reimbursement of drugs (**Figure 1 and Table 1**).
- Wide-ranging differences were seen in both; time taken by different HTA agencies for review of the same drug, and for a HTA agency to perform their review for different Novartis drugs. These differences were seen in the clinical evaluation of the drug and also in the overall time for HTA assessment (**Figure 1 and Table 1**).

Figure 1: Time for REA and final reimbursement criteria (from HTA start to final)



*EU Council Directive 89/105/EEC; known as "Transparency Directive"; Note: Countries in no particular order

Table 1: Duration of REA and HTA (in months)

Drug (Indication)	Fingolimod (RRMS)		Canakinumab[α] (CAPS)		Everolimus[β] (Breast Cancer)		Glycopyrronium bromide (COPD)	
Duration in months	For REA (approx.)	For total HTA	For REA (approx.)	For total HTA	For REA (approx.)	For total HTA	For REA (approx.)	For total HTA
UK	3	18	NA	18	3-4	10	3-4	4
Germany*	NA	12	NA	NA	NA	NA	NA	NA
France	3	7.5	4-5	9	7	24	3	12
Italy	3	8	7	13.5	3	12	6	8
Spain	1-2	5.2	NA	11.1	NA	8.2	NA	3.4
Sweden	NA	5	NA	NA	NA	NA	NA	9
Hungary	NA	34	NA	NA	Pending	Pending	1.5	11.4
Netherland	2-7	9	4	7	Pending	Pending	2	3
Poland	2	8.3	NA	NA	NA	1.5	NA	15.4
Czech Republic	2-3	16	NA	12	NA	14	NA	4

*No HTA as prior to AMNOG. [α]Sweden & Poland No dossier submitted for reimbursement. Hungary Reimbursement provided via a named patient system because of low patient number. [β]UK Negative assessment by NICE, funding achieved through Cancer Drugs Fund. Sweden: Everolimus approved for Renal cell carcinoma in September 2010, thus new indications were automatically approved.
NA, Not applicable no local REA done or no dossier submitted or REA not done separately or no HTA as prior to AMNOG (Product already in the market prior to 2011). Pending, at the time of this study; REA, relative efficacy assessment; CAPS, Cryopyrin-Associated Periodic Syndromes; COPD, Chronic Obstructive Pulmonary Disease; RRMS, Relapsing-Remitting Multiple Sclerosis
Note: Countries in no particular order

- Further, major differences in the acceptance of key clinical parameters such as comparators, subgroups and endpoints were observed, leading to differences in rating of clinical relevance and reimbursement criteria across countries (**Table 2**).
- This led to the requirement of additional data from companies and analyses such as indirect comparison and network meta-analysis, which contributed to the delay in time to patient access. E.g.:
  - In fingolimod; the endpoints accepted by UK were annual relapse rate, disability progression and MRI lesions. However, Germany and Czech Republic did not accept MRI lesions and disability progression, respectively. Furthermore, to assess efficacy in Rapidly Evolving Severe RRMS (RES-RRMS) subgroup, an indirect comparison resulted in 'small additional benefit' rating in Germany and subsequent recommendation. In UK, both indirect and mixed treatment comparisons were undertaken but the drug was not recommended for RES-RRMS subgroup (**Table 2**).

Table 2: Differences in clinical parameters for Fingolimod and Everolimus

Agency	Medical Value (=Therapeutic Benefit)	Endpoints	Target Population	Comparators
Fingolimod				
EU (EMA)	-	Relapse rate, MRI lesions, disability progression	Active RRMS	Placebo and beta-interferon
UK (NICE)	**Recommended as an option for RRMS group, but not recommended for RES RRMS subgroup**	Same as EMA label	**Asked for indirect comparison and mixed treatment comparison in RES-RRMS and active RRMS**	**Suggested to include other interferons**
France (HAS)	ASMR IV (minor improvement)	Same as EMA label	Same as EMA label	**Asked for comparison with natalizumab**
Germany (IQWIG)	**No additional benefit for RRMS group, but recommended for RES RRMS subgroup due to small additional benefit**	**Did not consider MRI lesions as end point**	**Asked for indirect comparison in RES RRMS subgroup**	**Did not accept placebo as the comparator**
Spain	Regarded as potential innovation	Same as EMA label	Same as EMA label	Same as EMA label
Italy (AIFA)	Regarded as potential innovation	Same as EMA label	Same as EMA label	Same as EMA label
Others	**Poland – additional benefit accepted and reimbursed only for RRMS Sweden – no additional benefit or added therapeutic value**	**Czech Republic – did not consider disability progression as one of the endpoints**	-	-
Everolimus				
EU (EMA)	-	Progression free survival (PFS) and overall survival (OS)	Hormone receptor-positive, HER2/neg negative advanced breast cancer	Placebo + Exemestane
UK (NICE)	Not recommended	Same as EMA label	Same as EMA label	**Demanded network meta-analysis with additional comparators** – Everolimus and Exemestane vs Fluvestrant.
France (HAS)	ASMR V (No clinical improvement)	Same as EMA label	**Major disagreements and prolonged discussions on target population**	**Major disagreement on choice of comparator**
Italy (AIFA)	**Reimbursed only for 24 months in specific patients**	Same as EMA label	Same as EMA label	Same as EMA label
Others	Poland –no additional benefit	**Czech Republic – did not consider disability progression as one of the endpoints**	-	-

Note: Countries in no particular order

Interview with Novartis Country Organisations

- To understand the impact a standardised Europe-wide REA could have on assessment of new drugs, Novartis associates were asked about the expected change such a system could bring to the overall HTA process if it would effectively replace the REA currently done at a country-level (Individual country responses for EU5 detailed in **Table 3**).
- Majority of them said that a standardised REA could reduce time to patient access by an average of 3-4 months and improve the transparency of the HTA process.

Table 3: Feedback from internal Novartis Country Organisations

Countries		Implications and expectations
UK	**UK**	▪ A harmonized REA may reduce the current resources spent on HTA in terms of less consultations and discussions about the clinical evaluation ▪ Duplication of REA can only be avoided if the pan EU REA meets high quality standards
Spain	**Spain**	▪ Pan EU REA will be instrumental to improve the time lines and efforts currently needed to produce the IPT (National Therapeutic Positioning Report)
Italy	**Italy**	▪ Reduction of efforts and costs involved in the clinical evaluation of the Scientific Technical Commission ▪ May accelerate the pricing process ▪ Could accelerate HTA at regional level, but not replace it
Germany	**Germany**	▪ Potential reduction in costs due to a reduced need for additional trials, possible avoidance of extra statistical analysis such as indirect comparisons ▪ Reduction in the effort to develop and review HTA submissions
France	**France**	▪ Can reduce the time needed for the clinical assessment, particularly if the pan EU REA leads to a rating of added therapeutic benefit (which could replace the ASMR)

Note: Countries in no particular order

Non-Novartis drugs:

- When analysing drugs launched by pharmaceutical companies other than Novartis; the findings indicate similar trends.
- Agencies showed differences in their acceptance of the additional therapeutic benefit for various reasons (**Box 1**).

Box 1: Examples of differences in REA in HTA decisions for Non-Novartis drugs

Linagliptin[1,5]

The most important difference observed for the reason in not accepting clinical efficacy of linagliptin was seen in the choice of comparator. This difference of opinion of IQWIG/GBA was an important example that reflected stark inter-country variations in HTA assessments. While linagliptin was recommended with restrictions in Scotland, as SMC found similar or comparable efficacy for the drug; HAS did not recommend the drug due to lack of sufficient evidence on drug efficacy.

Pertuzumab[1–4]

Variation in efficacy based decision in this case represents variation within two HTA bodies of the same country. IQWIG accepted overall survival (OS) as an endpoint, but was uncertain on safety and ruled "minor benefit" for the drug. GBA however recommended it as an add-on therapy distinguishing by the patient sub-group (patients with metastatic or locally recurrent unresectable HER2-positive breast cancer). HAS and SMC accepted the efficacy of the drug based on substantial added benefit, but SMC rejected the drug due to lack of robust economic results.

Sofosbuvir[6,7]

Has been at the centre of payor debate despite of undisputed efficacy and safety profile. IQWIG recommended the drug for only HCV genotype-2 whereas ZIN (Netherlands) recommended it for genotype-1 and 4. **Sofosbuvir analysis also reflects variation in HTA decision over a period of time by NICE**. Initially NICE rejected the drug, followed by a positive decision for only one HCV genotype. Later, NICE laid down complex guidelines regarding the various patient sub-groups who could access the drug, which was restricted only to a few HCV genotypes. Furthermore, the patients with severe liver disease alone could access sofosbuvir.

CONCLUSIONS

- Differences in clinical evaluation of the same drug by different HTA agencies leads to redundancies through repetitive clinical assessment based on same evidence submission. This contributes to an increase in time to patient access and additional investment of resources at both pharmaceutical company and HTA agency level.
- Our interviews confirm expectations that harmonized REA has the potential to reduce time to patient access and improve likelihood of meeting the EU requirement, strengthen the equity of care and increase predictability of expectations from pharmaceutical companies' research programmes.
- This study deepens our understanding of the limitations of the current way therapeutic benefit is assessed in Europe and the benefits that may result from a harmonized pan EU assessment of relative efficacy.

DISCUSSION AND FURTHER RESEARCH NEEDS

- The products we have analyzed show the diverging views HTA agencies currently have in regards to clinical parameters such as trial design, endpoints or relevant patient populations. Systematically diverging views about such clinical parameters can confuse patients, physicians and pharmaceutical manufacturers alike. The hypothesis is that this negatively impacts decision making capacity of both the manufacturers and users of medical technology.
- In addition, when HTA agencies systematically reach different conclusions about matters related to the clinical parameters of pharmaceuticals, there is a possibility that the credibility of these HTA agencies and the wider HTA system is diminished.
- These hypotheses could be tested by further research.

REFERENCES

1. IQWIG, *Pertuzumab: hint of major added benefit*. July 2013.
2. HAS, *TRANSPARENCY COMMITTEE Opinion - PERJETA 420 mg, concentrate for solution for infusion* July 2013, HAS.
3. SMC. *pertuzumab (Perjeta®) is not recommended for use within NHS Scotland.* October 2013 [cited 2015; Available from: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/897_13_pertuzumab_Perjeta/pertuzumab_Perjeta.
4. HAS. *TRANSPARENCY COMMITTEE OPINION - TRAJENTA 5 mg, film-coated tablets*. June 2012 [cited 2015; Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-02/trajenta_ct_11905.pdf.
5. SMC. *linagliptin (Trajenta®) is accepted for use within NHS Scotland*. May 2015 [cited 2015; Available from: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/850_13_linagliptin_Trajenta/linagliptin_Trajenta_Resubmission.
6. Global, I., *Netherlands' ZIN includes three drugs in national reimbursement list, HCV drug Olysio approved*, in *IHS Same Day Analysis*. November 2014.
7. Rampuria, N.R.a.A., *Sovaldi :The Story so Far*, in *GPMA Lunch and Learn*, N.R.a.A. Rampuria, Editor. 2014.

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