FRENCH HEALTH TECHNOLOGY ASSESSMENT OF DRUGS APPROVED UNDER EXCEPTIONAL CIRCUMSTANCES

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INTRODUCATION

- Approval under exceptional circumstances (EC) is a type of marketing authorisation granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical[1].
  - Approval under EC allows a faster patient access to innovative treatment despite incomplete clinical data [2].
- However, the absence of a robust evidence package for the demonstration of treatment advantages at the time of market approval posed great challenges for Health Technology Assessment (HTA) body to determine the extent of clinical benefits[3].
- The French Health Authority (Haute Autorité de Santé [HAS]) is an agency that makes technical advice for the inclusion of a pharmaceutical on the positive reimbursement list [4] (Table 1).

Table 1. The HAS assessment for the products value

AB level	Criteria for AB
Major	• Disease severity; • Efficacy /safety; • Position in the therapeutic strategy; • Impact on public health; • Type of treatment (preventive, curative or symptomatic)
Important	
Moderate	
Weak	
Insufficient	
IAB level	**Criteria for IAB**
I: Major	• Assessment by indication vs. comparators or therapeutic strategy; • Benefit mainly driven by the effect size of the incremental clinical efficacy benefit; • Safety and Quality of life considered if substantial disease burden
II: Important	
III: Moderate	
IV: Minor	
V: No improvement	

AB: Actual benefit; IAB: improvement in actual benefit

OBJECTIVE

- This study aimed to investigate the HAS assessment for the drugs approved under EC in the European Union (EU) with respects to actual benefit (AB) and improvement in actual benefit (IAB) by HAS.
- The impact of study methodology in pivotal trials on HAS recommendation was explored.

METHOD

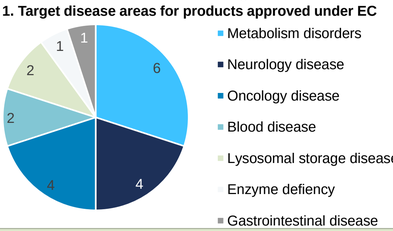
- The products granted with approval under EC until June 30th, 2019 were identified from European Medicines Agency (EMA) website[5].
  - Products withdrawn from EU market were excluded.
  - The target disease areas and orphan drug designations for approved products were identified.
- The latest HTA reports for each product approved under EC published by HAS were reviewed[6]. Results for the evaluation of AB and IAB for each product were extracted.
  - The rationales behind HAS recommendations were explored.
  - The main characteristics of pivotal studies (i.e. design, comparator) were extracted.

RESULTS

1. Characteristics of products approved under EC

- A total of 34 drugs were approved under EC until June 2019, among which, 6 drugs were withdrawn from the EU market, and 8 drugs had no HAS assessment available. Therefore, the HTA reports released by HAS for 20 drugs were reviewed:
  - All products held orphan drug designations with the exception of two products: Lojuxta® (Lomitapide) for the treatment of homozygous familial hypercholesterolemia and Vedrop® (Tocofersolan) for the treatment of vitamin E deficiency.
  - Metabolic diseases represented the disease area with the largest number of products approved under EC, followed by neurological disease and oncology. The target disease areas for the approved products are presented in Figure 1.

Figure 1. Target disease areas for products approved under EC



2. Results for the evaluation of actual benefits

- AB was appraised as ‘important’ for 60% of the drugs approved under EC (12 out of 20 drugs) (Table 2).
  - 9 drugs had non-comparative pivotal trials, 1 drug had before-after comparative pivotal trial, and 2 drugs had randomised, double-blind, placebo controlled pivotal trials.
- AB was appraised as ‘moderate’ for 25% of the drugs approved under EC (5 out of 20 drugs) (Table 2).
  - 4 drugs had randomised, double-blind, placebo controlled pivotal trials, and 1 had historical cohort pivotal trials.
- AB was appraised as ‘weak’ for 5% of drugs approved under EC (1 out of 20 drugs) (Table 2).
  - It used retrospective analysis of the medical records of 3 patients cohorts and one literature review as pivotal evidence.
- Only two drugs: Kolbam® (Cholic acid) and Raxone® (Idebenone) were assessed with ‘insufficient’ actual benefit, therefore they were not recommended for reimbursement:
  - The pivotal clinical studies for Kolbam® were two open-label non-comparative studies, the level of evidence was judged quite low. There was uncertainty in the drug efficacy in cerebrotendineous xanthomatosis, especially on neurological symptoms.
  - The efficacy of Raxone® was demonstrated using post-hoc analyses of efficacy data from the pivotal study, the level of evidence therefore was very low. In the absence of demonstration of its efficacy, Raxone® was considered having no role in the therapeutic strategy.

3. Results for the evaluation of improvement in actual benefits

- IAB was appraised as ‘major (I)’ for 1 product, as ‘important (II)’ for 3 products, as ‘moderate (III)’ for 2 products, as ‘minor (IV)’ for 9 products, and as ‘no improvement (V)’ for 3 products (Table 2).
- Despite the fact that only non-comparative study was available as key evidence, 5 products were assessed with IAB level of I/II/III for the following considerations:
  - 3 products (Evoltra®; Atriance®; Orphacol®): were indicated in the diseases with high unmet clinical needs, where there was no other therapeutic alternative.
  - 2 products (Brineura® and Strensiq®): Brineura® showed a clinical benefit in terms of motor languages score and stabilisation of qualify of life. Strensiq® showed a favourable outcome in respiratory function.
- With regards to 12 products assessed with IAB level of IV/V, HAS showed concerns in the following aspects:
  - 8 products (Qarziba®; Obizur®; Lojuxta®; Vyndaqel®; Lamzede®; Ceplene®; Elaprase®; Chenodeoxycholic acid Leadiant): were associated with insufficient efficacy evidence or long-term efficacy cannot be assessed by HAS.
  - 4 products (Qarziba®; Increlex®; Vyndaqel®; Lamzede®): were concerned with unfavourable safety profile.
  - 10 products (Defitelio®; Vedrop®; Firdapse®): were criticized with questionable methodology used in the pivotal studies: small patients number, high rate of lost to follow-up, high heterogeneity among patients and lack of control group. Therefore, the low quality of evidence made it difficult to demonstrate an improvement in added benefit over the standard of care.

Table 2. Results for the evaluation of AB and IAB

IAB level	Drug name	AB level*	Study design of pivotal trials
I	Orphacol®	Important	Non-comparator study; data from Orphanet database; literature data;
II	Atriance®	Important	Non-comparative study
	Evoltra®	Important	non-comparative study
	Strensiq®	Important	Non-comparative study
III	Brineura®	Important	Non-comparative, open-label dose escalation study
	Naglazyme®	Important	Randomised double-blind placebo controlled study
IV	Defitelio®	Moderate	Historical cohort study
	Elaprase®	Important	Placebo-controlled, randomised, double-blind study
	Firdapse®	Moderate	Two placebo-controlled randomised, double blind crossover study
	Increlex®	Important	Non-comparative study
	Lamzede®	Moderate	Randomized, double-blind, placebo controlled study.
	Lojuxta®	Important	Non-comparator study
	Qarziba®	Important	Non comparative study
	Vedrop®	Important	Open-label, before-after study
	Vyndaqel®	Moderate	Randomized, double-blind, placebo controlled
V	Ceplene®	Moderate	Open-labelled, randomised, control study versus no treatment
	Chenodeoxycholic acid Leadiant	Weak	1) Retrospective analysis of the medical records; 2) literature review
	Obizur®	Important	Non-comparator study

AB: Actual benefit; EC: Exceptional circumstance; IAB: Improvement in actual benefit
* No product was evaluated with ‘Major’ actual benefit

CONCLUSIONS

- Products approved under EC have likely an opportunity to receive positive recommendations for reimbursement in France.
- Products indicated in the rare diseases without therapeutic alternatives have the great potential to be evaluated with significant improvement in actual benefit [8].
- Limitations in the study methodology, such as non-comparative, open-label study, insufficient evidence for drug efficacy, unfavourable safety profile were considered by HAS as main limitations to address, despite positive recommendations for reimbursement issued.

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