Are there differences between medicine appraisals in France in the paediatric versus the adult populations ?

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BACKGROUND AND AIMS

The French National Authority for Health (HAS) is responsible for health technology assessment. The Transparency Committee (TC) of the HAS recommends the reimbursement of medicine by appraising two criteria:

- ▶ **the clinical benefit (CB):** assesses the intrinsic value of the drug
 - 3 levels of “sufficient CB” → **positive recommendation of reimbursement**
“important”/“moderate”/“mild”
 - 1 level of “insufficient CB” → **negative recommendation of reimbursement**
- ▶ **the clinical added value (CAV):** assesses the comparative value of the drug in comparison to available treatments
 - 5 levels → **Taken into account in price negotiations**
“major” (CAV I)/“important” (CAV II)/
“moderate” (CAV III)/“minor” (CAV IV)/“No CAV” (CAV V)

Hypothesis: more favourable TC assessment of paediatric drugs as compared to adult ones.

METHODS

- Retrospective study:**
1. Selection of TC appraisals concerning paediatric indications.
Periods: - 2015-2017 for appraisal
- > 2010 for marketing authorization
 2. Research of TC appraisals concerning adult for the same indication by medicine.
Periods: no limitation of date for appraisal and marketing authorization.
 3. Comparison of appraisals between paediatric and adult.

➔ **116 mixed indications (paediatric and adult) identified corresponding to 102 medicines**

RESULTS

Concerning CB, appraisals were similar in 94% (109/116) of the cases between paediatric and adult. CB was important in 90% (98/109) of the cases. (Figure 1).

Concerning CAV, a comparison of appraisals was made for 105/116 indications (9 had an insufficient paediatric’s CB and 2 adult’s CAV were not available). CAV were similar in 90% (94/105) of the cases. “No CAV” was identified in 80% (75/94) of the cases (Figure 2).

Discrepancies (7/116): 5/7 in favour of adult ; 2/7 in favour of paediatric (Table 1).

Table 1. Molecules and indications concerned by a different CB (n=7/116 indications)

MOLECULE	INDICATIONS	THERAPEUTIC AREA	LEVEL OF CB	
			PAEDIATRIC (Main reason)	ADULT
INFERIOR CB (PAEDIATRIC < ADULT) (n = 5)				
Oseltamivir	Influenza	Infectiology	Insufficient (child < 1 year) - (lack of data)	Mild
Dolutegravir	HIV treatment (integrase inhibitor resistance)		Insufficient (lack of data)	Important
Immunoglobulin	Immunodeficiency syndrome	Immunology	Insufficient (lack of relevant data)	Important
	Hypogammaglobulinaemia pré/post AHSCT			
Étanercept	Psoriasis	Dermatology	Moderate (moderate efficacy vs placebo + uncertainty about long term safety)	Important
SUPERIOR CB (PAEDIATRIC > ADULT) (n = 2)				
Alglucosidase alfa	Pompe disease	Endocrinology/ Metabolism	Important in specific populations : - infantile-onset disease (Pompe disease) - neonates with rapidly progressive deficiency (LAL deficiency) (high severity of disease + important efficacy + no alternative)	Mild
Sébélipase alfa	LAL deficiency			

AHST: allogeneic hematopoietic stem cell transplantation, HIV: human immunodeficiency virus, LAL: lysosomal acid lipase

Discrepancies (11/105): 7/11 in favour of adult ; 2/11 in favour of paediatric ; 2/11 in between CAV (Table 2).

Table 2. Molecules and indications concerned by a different CAV (n=11/105 indications)

MOLECULE	INDICATIONS	THERAPEUTIC AREA	LEVEL OF CAV	
			PAEDIATRIC (Main reason)	ADULT
INFERIOR CAV (PAEDIATRIC < ADULT) (n = 7)				
Entecavir	HBV infection	Infectiology	IV (superiority vs placebo + few alternatives)	II
Raltegravir	HIV-1 infection		IV (child 4 weeks to 2 years) (non-comparative study + no alternatives)	III
Palonosetron	Nausea/vomiting of CT	Gastroenterology	V (non-inferiority efficacy vs ondansetron)	IV
Ursodeoxycholic acid	Cystic fibrosis-related liver disease	Hepatology	V (superiority vs placebo + lack of transposability)	II
Ustekinumab	Psoriasis	Dermatology	V (superiority vs placebo)	IV
Travoprost	Ocular hypertension/ glaucoma	Ophtalmology	V (non-inferiority vs timolol)	III
Latanoprost				II
SUPERIOR CAV (PAEDIATRIC > ADULT) (n = 2)				
Alglucosidase alpha	Pompe disease	Endocrinology/ Metabolism	III (infantile-onset disease) (significant need + efficacy on OS vs historical cohort)	IV (late-onset disease)
Sébélipase alpha	LAL deficiency		III (neonates with rapidly progressive deficiency) (significant need + efficacy on OS vs historical cohort)	V
IN BETWEEN CAV (n = 2)				
Eltrombopag	Immune thrombocytopenic purpura	Hematology	III (significant need + disease management)	Splenectomised (II) or not (IV)
Aprépitant	Nausea/vomiting of CT	Gastroenterology	III (superior efficacy vs placebo + safety + impact on QOL)	Moderate (V) or high (III) emetogenic

CT : chemotherapy, HBV: hepatitis B virus, HIV: human immunodeficiency virus, LAL: lysosomal acid lipase, OS: overall survival , QOL: quality of life

CONCLUSIONS

Between 2015 and 2017 for paediatrics, more than 90% of the assessment of the Transparency Committee of the French National Authority for Health (HAS) were similar between paediatric and adult indications with a high proportion of “no CAV”, although a lower level of evidence in paediatrics. Among few discrepancies observed (< 10%), mainly less favourable appraisals were given in paediatrics because of a lack of relevant data, superiority vs placebo or non-inferiority design studies. A more favourable appraisal were given for two medicines in paediatrics (alglucosidase alfa and sébélipase alfa) in endocrinology/metabolism because of a significant need in a high severity disease. HAS is thinking about how to support companies for a more and better development in paediatrics.