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Analysis of NICE and US ICER HTA Outcomes for Ultra-Orphan Medicinal Products

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BACKGROUND

- Ultra-orphan drug is a specific classification of drugs used to treat extremely rare diseases that are chronically debilitating or life-threatening. Due to low prevalence of the conditions and associated complications such as the lack of standardized patient-centred outcome measures or usual care, the assessment of ultra-orphan drugs present a challenge for HTA bodies [1,2].
- The National Institute for Health and Care Excellence (NICE) in the UK and the Institute of Clinical and Economic Review (ICER) in the US adapted their HTA frameworks to better capture value of drugs for ultra-rare diseases.
  - Aside of the single technology appraisal (STA) programme NICE has implemented the Highly Specialised Technologies (HST) programme which is used for the assessment of ultra-orphan drugs meeting certain eligibility criteria. The programme uses significantly higher cost-effectiveness thresholds (£100,000-£300,000, depending on QALY gain) compared to the STA (usually £20,000-£30,000) to guide recommendations of the Evaluation Committee [4,5].
  - ICER has adopted higher willingness-to-pay thresholds ($50,000-$500,000 and additional societal perspective for the economic evaluation of ultra-orphan drugs to give potential payers a wider perspective for the decision. However, thresholds used for deriving value-based price (VBP) benchmarks, price rebates and final conclusions remained unchanged compared to the standard approach ($100,000 and $150,000) [3].

OBJECTIVES

- The objective of this study was to analyse actual outcomes from NICE and ICER frameworks for ultra-orphan products, which have been assessed by both HTA bodies.

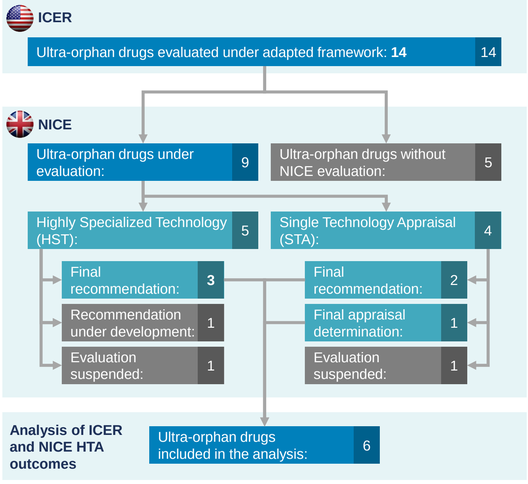
METHODS

- US ICER reports for drugs evaluated with the framework modified for ultra-orphan drugs (adapted in 2017) were obtained from ICER's website. To allow comparative assessment, HST reports for the same drugs were searched on the NICE website. In case HST reports were not found, a subsequent search was conducted to check if the drug was assessed under STA.
- The search of HTA reports was conducted in June 2019 and was updated in October 2019.
- Identified reports have been analysed in terms of information on reaching the cost-effectiveness/VBP thresholds, and eventual rebates for ICER, or recommendations for NICE.

RESULTS

- A total of 14 ultra-orphan drugs were evaluated by ICER after adoption of the modified framework in 2017. Among them, 9 drugs had a corresponding NICE technology appraisal process - 5 under HST programme and 4 under STA programme. However, NICE recommendations were available for 6 products (5 products had final recommendation and 1 product had a final appraisal determination), while the procedure for the remaining products was suspended (2 products) or the appraisal was under development (1 product) (Fig. 1).

Figure 1. Identification of ultra-orphan drugs with corresponding assessments in ICER and NICE



- Despite modifications adopted in ICER framework for ultra-orphan drugs, all 6 analysed products were found not cost-effective considering the standard willingness-to-pay thresholds ($100,000 and $150,000) but also the extended threshold of $500,000. (Tab. 1)
- It is important to note that the outcomes of the threshold analysis involving thresholds up to $500,000 are provided only in full ICER reports, however the final determination of the drug cost-effectiveness, as well as calculation of VBP benchmarks is based on standard thresholds of $100,000 and $150,000.
- Due to the lack of cost-effectiveness, prices of all drugs would require significant discounts to reach the VBP benchmarks. Considering the standard thresholds, the lowest discount would be required for lanadelumab used in hereditary angioedema (34%), while the highest in case of drugs used in hereditary transthyretin-related amyloidosis - inotersen and patisiran (respectively 97-94% and 95-90%, depending on the threshold).
- Based on ICER's assessment outcomes, independent voting committees voted for the long-term value for money of the drugs. For almost all of the analysed ultra-orphan products the committee members voted unanimously or in majority for low value, mainly due to very high cost of therapies. The exception was gene therapy voretigene neparvovec indicated for the treatment of inherited retinal disease. It was considered by the majority of the committee members as demonstrating moderate long-term value for money, mainly due to potential long term durability of effect and novel mechanism of action. (Tab. 1)
- Contrary to the ICER, majority of ultra-orphan drugs assessed by NICE (4 of 6) was considered as cost-effective treatment option. Three of them were assessed under HST programme, with incremental costs-effectiveness ratio below or around the cost-effectiveness threshold. However, the threshold for voretigene neparvovec was increased by 1.2 in accordance with the rule of the HST programme, which allows to increase the threshold proportionally to additional QALY, if the gain is between 10 and 30. One drug (lanadelumab) was assessed under STA, with the incremental cost below £20,000. (Tab. 1)
- The NICE assessment resulted in positive recommendations for all drugs which demonstrated cost-effectiveness and also for nusinersen, where the economic evaluation did not allow fully determine its cost-effectiveness due to high uncertainties around the incremental cost-effectiveness ratio. However, in this case the decision was made after considering additional factors such as potential benefits not captured by the model and the managed access agreement, which reduced the risk for the payer.

Table 1. ICER and NICE Assessment outcomes for ultra-orphan drugs

Drug (indication)	ICER		NICE	
	Price below VBP benchmark? *Discount required* (*$100k|150k|500k*)	Long-term value for money	Incremental cost below threshold? *Programme*	Recommended ?
Inotersen (hATTR)	No | No | No *97% | 94% | 77%*[1]	Low	Yes *HST*	Yes
Patisiran (hATTR)	No | No | No *95% | 90% | 56%*	Low	Range around threshold *HST*	Yes
Lumacaftor/ ivacaftor (CF)	No | No | No *75% | 71% | 39%*	Low	No *STA*	No
Nusinersen (SMA)	No | No | No *90% | 83% | 31%*	Low	Uncertain[2] *STA*	Yes
Voretigene neparvovec (IRD)	No | No | No *82% | 75% | 22%*	Moderate	Range around threshold *HST*	Yes
Lanadelumab (HA)	No | No | No *33% | 32% | 30%*	Low	Yes[2] *STA*	Yes[3]

1. Inotersen price not available at the time of assessment, assumed to be equal to the price of patisiran;
2. Exact incremental cost not reported 3. Recommended with population restrictions & final appraisal determination;
CF - cystic fibrosis; HA - hereditary angioedema; hATTR - hereditary transthyretin-related amyloidosis; IRD - inherited retinal disease; SMA - spinal muscular atrophy; VBP – Value Price Benchmark; HST - Highly Specialised Technology programme; STA – Single Technology Appraisal; QALY – quality adjusted life years.

CONCLUSIONS

- While both organizations included special adaptations for ultra-orphan drugs to their assessment frameworks, drugs are less commonly qualified for the dedicated programme in NICE than for ultra-orphan framework in US ICER. However, despite the use of specific criteria, demonstration of cost-effectiveness under the ICER framework still represents a significant challenge due to very high cost of the therapies.
- In the UK, the HST pathway may increase chances for positive outcome, especially if a drug has a potential for a significant QALY gain (10-30), which allows to increase further the cost-effectiveness threshold. However, if an ultra-orphan drug does not qualify for HST, it could still be positively evaluated under standard STA.
- What is more, some presented cases proved that even if cost-effectiveness analysis reveals incremental cost-effectiveness ratios exceeding the range accepted by NICE, the final recommendation still might be positive, however providing discounts and/or population restrictions are implemented.

REFERENCES
1. NICE Citizens Council Report. Ultra-orphan drugs. National Institute for Health and Care Excellence, London, November 2004.
2. ICER. Assessing the Effectiveness and Value of Drugs for Rare Conditions. May 2017.
3. ICER. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. Final Version. 2017.
4. MAP BioPharma. Access to Orphan Medicines: A Case for Change. 2019.
5. NICE. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. National Institute for Health and Care Excellence. April 2017.

ISPOR 2019, Copenhagen, Europe, November 2-6 2019. PRO108.