Cystic fibrosis therapies: key drivers behind differing HTA decisions

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Introduction

- Cystic Fibrosis (CF) is a chronic, inherited condition affecting multiple organs, resulting in early mortality.
- A dysfunctional protein, the cystic fibrosis transmembrane conductance regulator (CFTR), alters mucous consistency throughout the body, increasing risk of lung infections and other problems.
- Patients with CF are burdened with lifelong, time-consuming, daily treatments aimed at symptom relief.
- Two therapies developed by VERTEX for CF have been assessed by Health Technology Assessment (HTA) organisations in Europe; ivacaftor and ivacaftor-lumacaftor. These drugs are indicated for a range of CF populations categorised by the specific mutation affecting the CFTR protein (see **Table 2**).
- The European Medicines Agency (EMA) states that CF affects roughly 0.8/10,000 people in Europe (a total of around 41,000/511,100,000); classifying CF as an orphan disease (5 people in 10,000)[1].
- Orphan diseases pose challenges for HTA. Organised clinical trials have small patient populations, and high drug prices are necessary to recoup high research and development costs.
- **Table 1**[2-5] shows the differing key criteria for assessment of orphan drugs by several HTA organisations; National Institute of Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA) and Scottish Medicines Consortium (SMC).

Table 1: Criteria for assessment of drugs for rare diseases

HTA body	Key assessment criteria

NICE	• Orphan drugs (< 5/10,000), standard ICER threshold.
	• Special assessment for ultra-orphan drugs (< 1/50,000).
	  • Clinical benefit for patients and carers, if relevant.
	  • CE threshold of £100,000/ QALY. Incremental QALY weighting (1, 1 - 3, and 3) for incremental QALY gains (≤10, 10 to 30, and >30).
	  • Innovation considered; MAA may be requested.
	• Commercial discussions if BI > £20 million/ year.

HAS	• Additional benefit 'proven at MA ' if BI <€30 million/ year. • Accelerated procedure for innovative therapy. • If BI threshold exceeded, SMR and ASMR are assessed. • Follow-up research may be requested.
G-BA	• Additional benefit 'proven at MA' if BI <€50 million/ year. If BI > €50 million/ year, GBA will re-assess benefit. • EAMB assessed. • IQWiG assess number of eligible patients and costs. • Follow-up data may be requested.
SMC	• Additional PACE meeting (orphan and ultra-orphan). • Specific framework of decision making criteria (ultra-orphan drugs only).

Objectives

- Despite similar unmet needs in these nations, health technology assessment (HTA) decisions have varied.
- We aim to:
  - Summarise HTA decisions.
  - Explore reasons they differ.

Methods

Searches were conducted up to the 31st May 2018 for all publicly available HTA reports of ivacaftor and ivacaftor-lumacaftor. Reports were identified and analysed across:

- NICE
- HAS
- G-BA
- SMC
- HSE
- AWMSG

Results

- Ivacaftor and ivacaftor-lumacaftor were initially granted orphan drug status by the EMA[1,7]. This was withdrawn for the latter[7] following a request by the marketing authorisation (MA) holder.
- As shown in **Figure 1**, amongst the countries studied:
  - Germany has the lowest prevalence of CF at 0.87/10,000.
  - Ireland has the highest at 2.98/10,0000.
  - The United Kingdom (UK) has the second highest prevalence at 1.61/10,0000 people; England (1.6/10,000), Scotland (1.7/10,000) and Wales (1.3/10,000)[9].
- As shown in **Table 1**, each of the countries assess orphan drugs differently. NICE have special assessment criteria for ultra-orphan and highly specialised technologies (HSTs), but not orphan drugs.

Figure 1: Estimated prevalence (per 10,000) of CF across Europe[8]

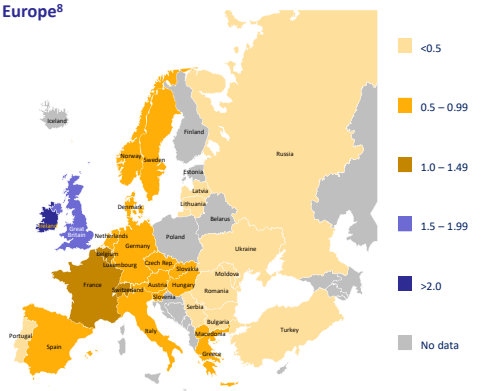

Table 2: Summary of HTA decisions

Drug	Ivacaftor				Ivacaftor-lumacaftor
Indication (age; mutation)	*> 6 years; G551D*	*> 6 years; G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*	*> 18 years; R117H*	*> 2 years; G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*	*> 12 years; 2 x F508del*
Orphan/ ultra orphan status	- ✓ ✓ ✓ Unknown ✓	- - ✓ ✓ Unknown ✓	- ✓ - ✓ Unknown ✓	- ✓ ✓ ✓ Unknown ✓	✗ ✓ ✓ ✗ Unknown -
PPPY cost	- £182,000 - €289,060 - -	- - - €271,482 - -	- £182,000 - €268,770 - -	- £182,000 - €268,770 - -	£104,000 £104,000 - €195,884 - -
Decision	- ✗ ✓ ✓ ✓ ✗	- - ✓ ✓ ✓ ✓	- ✗ - ✓ ✓ ✓	- ✗ ✓ ✓ ✓ ✓	✗ ✗ ✓ ✓ ✓ -

HTA decisions, summarised in Table 2[10-29]

G-BA reviewed ivacaftor as an orphan drug. Additional medical benefit was considered proven for all indications but extent of additional medical benefit (EAMB) ranged from low/ non-quantifiable to considerable. Ivacaftor-lumacaftor was not assessed as an orphan drug but had additional medical benefit and EAMB was considerable.

SMC did not recommend either drug, despite the use of orphan/ ultra-orphan criteria. Base case ICERs/QALY compared to standard of care (SOC) ranged from £277,011 – £609,316 (ivacaftor) and £310,879 (ivacaftor-lumacaftor). Governmental schemes have since allowed ivacaftor to be available.

AWMSG did not review ivacaftor-lumacaftor following a negative recommendation from NICE. Their initial negative recommendation of ivacaftor was overruled by the Welsh Government and AWMSG have since approved all other indications for ivacaftor.

HAS recommended ivacaftor for three separate indications in CF, with an SMR of substantial and an ASMR of II (important). They approved ivacaftor-lumacaftor with an SMR of substantial and an ASMR of IV (minor), suggesting a price negotiation prior to approval.

NICE did not appraise ivacaftor and did not approve ivacaftor-lumacaftor. The company base case ICER/QALY compared to SOC was £218,248. The ERG produced a conservative assumption ICER of £272,265; exploratory analysis gave an ICER of £221,992 and sensitivity analysis ranged from £135,464 – £459,045. The committee concluded that the ICER lay outside of the range considered a cost-effective use of NHS resources.

HSE has recently approved all VERTEX CF therapies through a confidential novel pipeline deal.

Conclusion

It appears that prevalence of CF may be an important factor in decision making amongst several European countries. Although HTA organisations which have special criteria for assessing orphan drugs have generally approved VERTEX's innovative medicines (France and Germany), this is not a consistent pattern; for example, the SMC did not recommend.

In lower prevalence countries such as Germany, the benefit from an orphan drug policy could be realised, whilst in higher prevalence countries like Ireland, there was pressure to focus on CF as a national priority, meaning that payers and VERTEX have worked together to agree innovative pricing solutions allowing patients access to treatment.

Abbreviations: ASMR, clinical added value; AWMSG, All Wales Medicines Strategy Group; BI, Budget Impact; CE, Cost-Effectiveness; CF, Cystic Fibrosis; CFTR, Cystic Fibrosis Transmembrane conductance Regulator; EAMB, Extent of Additional Medical Benefit; EMA, European Medicines Agency; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HSE, Health Service Executive; HTA, Health Technology Assessment; ICER, Incremental Cost Effectiveness Ratio; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MA, Marketing Authorisation; MAA, Managed Access Arrangement; NICE, National Institute for Health and Care Excellence; PPPY, per patient per year; SMC, Scottish Medicines Consortium; SMR, actual clinical benefit; SOC, Standard of Care; QALY, Quality Adjusted Life Year; UK, United Kingdom.

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