Pricing of innovative medicines: do innovative schemes offer a solution?

Caroline von Wilamowitz-Moellendorff[1], Kathy Kelly[1], James Wordsworth[1], Alistair Curry[2], Stephen Ralston[2]
[1]SIRIUS Market Access, Newcastle upon Tyne, United Kingdom
[2]SIRIUS Market Access, London, United Kingdom
Email: info@siriusmarketaccess.com

PND100

Introduction

- Cystic Fibrosis (CF) is a chronic, inherited condition affecting multiple organs and resulting in early mortality.
- Denmark has become the most recent European country (reported 1st October 2018) to reimburse ivacaftor-lumacaftor joining Sweden, Austria, Germany, Ireland, Italy and the Netherlands[1,2].

Situation in the UK

- The UK has the second largest CF population in the world[3]. Despite this, an agreement is still to be reached with VERTEX after 2 years of discussion since ivacaftor-lumacaftor was rejected by NICE in 2016[4].
- There has been much public pressure to reach an agreement, with multiple demonstrations and a parliamentary debate following an online petition gaining over 116,000 signatures[5].
- An estimated 200 people with CF have died since debates began[6].
- It has been argued that the unequal access to these medicines is unfair, particularly when those eligible for ivacaftor 'now enjoy a near-normal life because they are lucky enough to have a rare type of CF'[6].

Proposed UK deal

- VERTEX are asking for a deal covering reimbursement of its entire CF drug portfolio, including future drugs (similar to the deals made in Denmark, Sweden and Ireland)[1,2,5,7].
- National Health Service (NHS) England want to receive the entire package under the same overall budget they are already paying for ivacaftor (priced at £182,600/year)[5,8], thereby expanding the number of eligible patients from 450 to 5,000 for no extra funding[9].
- Pricing remains confidential, but in a letter from NHS England, the current deal on the table would see NHS England pay around £500 million over the next 5 years. VERTEX have commented that this would equate to approximately £14,000 per patient per year, reflecting an almost 90% discount[9].

Current situation

- VERTEX are no longer publicly engaging with NICE until the assessment procedure is changed; cost effectiveness (CE) thresholds applied by NICE are being described as not suitable for orphan diseases, and the approval process as 'an analogue process for a digital age'[10-12].
- Differing Health Technology Assessment (HTA) methods in Europe has lead to inequality in access to drugs for CF.

Objectives

- With NICE still to recommend ivacaftor-lumacaftor and the introduction of innovative pricing deals facing challenges, this analysis explores:
  - The NICE appraisal
  - Modelling outcomes issues in this patient population.
  - How these treatment options could be cost effective.
  - Whether there are merits in innovative pricing deals.

Methods

- We performed a review of the NICE HTA report for ivacaftor-lumacaftor to understand why it was not recommended.
- We developed our own basic model to assess how VERTEX could have made ivacaftor-lumacaftor cost effective.
- This model also helped us understand whether innovative pricing deals were the only realistic option, if original price points where to be maintained.

Results[4]

Company submission

- Data for the economic model came from two international, multicentre, phase 3, placebo-controlled randomised controlled trials, TRAFFIC (n=549) and TRANSPORT (n=559), and the UK CF registry.
- Assumptions and base case numbers used by the company are summarised in **Table 1.**

Evidence review group (ERG) and Assessment Committee (AC) response

- The ERG considered that because many of the parameters for the company's model came from the whole UK CF population, and not just the eligible patient population, there was some doubt over the clinical efficacy and cost-effectiveness results stated.
- Comments from the ERG and AC included:
  - There were difficulties combining trial and registry data.
  - There should be no price drop after 12 years.
  - Adherence rates should be 96.5%.
  - Stopping treatment after 24 weeks should be possible.
  - There were difficulties measuring HRQoL.
  - Percent predicted forced expiratory volume in 1 second (ppFEV1) improvement/ absolute change should be from 24 weeks and not 16 weeks.
  - ppFEV1 decline should be age dependent for all.
  - Pulmonary exacerbations (PEx) included only patients requiring intravenous antibiotics and hospitalization, causing uncertainty. Additionally, no long term evidence was provided to support the benefit assumption.
  - ppFEV1 improvement and pulmonary exacerbation improvement may not be independent.

Table 1: Assumptions and base case parameters

Inputs	Company	
	Lum-Iva + SOC	SOC alone
Cycle length	4-week for 1st 2 years then yearly	
Time Horizon	Lifetime	
Discount rates	3.5% for costs and health effects with a half cycle correction	
Baseline characteristics	TRAFFIC, TRANSPORT and UK CF registry	
Drug costs	89% decrease for L-I after 12 years	
Hospitalization costs	PEx reduced by 61% for L-I	
Adherence	90% for L-I	
Stopping treatment	6.8% stop L-I in first 24 weeks Nil after 24 weeks	
Age specific mortality	Derived from UK CF registry Adjusted for 9 characteristics	
Utility values	Post transplant: 0.81 Other: varied throughout time horizon	
ppFEV1		
• 16 – 24 weeks	Baseline + 2.8%	Baseline
• > 24 weeks (annual change)		
• < 18	- 0.68	- 2.34
• 18 – 24	- 0.68	- 1.92
• ≥ 25	- 0.68	- 1.45
PEx	IV antibiotics and hopsitalisation	
Annual rate of PEx (predicted)	ppFEV1 and age multiplied by 0.442	ppFEV1 and age
Weight for age z-score (BMI)	Baseline + 0.068	Baseline
Rate of lung transplant	24.7% of people with ppFEV1 < 30%	
Post lung transplant mortality	15.2% in 1st year 6.1% subsequent years	

Table 2: NICE HTA ICER results compared to standard of care

ICER/QALY	Company	ERG	Committee
Base case	£218,248	Conservative: £272,265 Exploratory: £221,992	Between £218,000 – £349,000 Considerably higher than CE threshold
Probabilistic	£214,833	-	-
Sensitivity/scenario/ subgroup	£159,678 – £300,688	Generic pricing: £203,100 - £330,385 Annual ppFEV1 decline: £135,464 - £459,045	-

- ICER per QALY results from the NICE HTA for ivacaftor-lumacaftor are shown in **Table 2.**
- Based on information from the NICE HTA for ivacaftor-lumacaftor, SIRIUS developed a model deriving a base case ICER of £217,771.
- Ivacaftor-lumacaftor's price needed to be reduced to £723,670, £481,445 and £446,840 to achieve ICERs of £100,000, £50,000 and £30,000 respectively.
- Altering the number of life years (LY) to 18.3162, 37.888 and 51.866, and the QALYs to 16.46, 34.04 and 46.60, also led to ICERs of £100,000, £50,000 and £30,000 respectively.
- If the original cost, LY, and QALYs all stayed the same, then to attain ICERs of £100,000, £50,000 and £30,000, the utility value would have to increase to values greater than 1.

Discussion

This research has identified many issues with the modelling of CF. The most obvious of these is the use of registry data to fill in trial data gaps. Trials would have to continue for decades before meaningful survival data was gathered. Estimates can be made from registry data, but it is unsure how meaningful/ reliable it is to extrapolate this data. As mentioned by the ERG in the NICE appraisal, HRQoL is also difficult to measure in this patient population who have only ever known life with CF. This makes measuring cost effectiveness by the traditional method unreliable.

Conclusion

Since 2016, NHS England have been in discussion with VERTEX to come to an agreement on ivacaftor-lumacaftor, and are sticking to NICE's recommendation that it is not cost-effective to support ivacaftor-lumacaftor. While NICE assess under the standard approach, there is very little leeway for these novel medicines. The required price reduction to meet traditional cost per QALY thresholds would be substantial and could disincentivise the development of further medications, and the utility value increments necessary to make ivacaftor-lumacaftor cost effective using the original costs, LYs and QALY gains may become impossible to achieve. Innovative pricing deals similar to those made in Sweden, Ireland, and Denmark would allow England to have access to all current and future CF drugs produced by VERTEX, whilst providing budget certainty to the NHS. The unique nature of VERTEX's range of medicines in CF would make this precedent difficult to replicate.

Abbreviations: AC, Assessment Committee; BMI, Body Mass Index; CE, Cost Effective; CF, Cystic Fibrosis; ERG, Evidence Review Group; HRQoL, Health Related Quality of Life; HST, Highly Specialised Technology; HTA, Health Technology Assessment; ICER, Incremental Cost Effectiveness Ratio; IV, intravenous; L-I, Lumacaftor-Ivacaftor; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PEx, Pulmonary Exacerbation; ppFEV1, percent predicted Forced Expiratory Volume in 1 second; pppy, per patient per year; QALY; Quality Adjusted Life Year; UK, United Kingdom.

References
1. FirstWord Pharma. 2018. 'Vertex Announces Access Contract in Denmark for current and Future Cystic Fibrosis Medicines', Accessed 26/10/18. http://www.firstwordpharma.com/print/1594450?tsid=17.
2. FirstWord Pharma. 2018. 'Vertex announces long-term access agreement in Sweden for cystic fibrosis medicine ORKAMBI (lumacaftor/ivacaftor)', Accessed 26/10/18. http://www.firstwordpharma.com/print/1573156?tsid=17.
3. ECFS. 2018. 'ECFS Patient Registry Annual Data Report 2016', *European Cystic Fibrosis Society*.
4. NICE [TA398]. 2018. 'Lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation', *National Institute for Health and Care Excellence*.
5. Pharmaphorum. 2018. 'Vertex and NHS close in on cystic fibrosis drug pricing deal', Accessed 26/10/18. https://www.printfriendly.com/p/g/SRrVSS.
6. Pharmaphorum. 2018. 'Patients call for end to two-year row over CF drug funding', Accessed 26/10/18. https://www.printfriendly.com/p/g/uMVThg.
7. FirstWord Pharma. 2017. 'Vertex Announces Long-Term Reimbursement Agreement with the Republic of Ireland for ORKAMBI (lumacaftor/ivacaftor), KALYDECO (ivacaftor) and Future Cystic Fibrosis Medicines', Accessed 26/10/18. http://www.firstwordpharma.com/print/1476672?tsid=17.
8. Pharmaphorum. 2018. 'Vertex says 'some way' to CF drug price deal after NHS meeting', Accessed 26/10/18. https://printfriendly.com/p/g/dH9RW9.
9. Selina McKee. 2018. 'Vertex mulls over NHS England's offer for CF drugs', PharmaTimes Online, Accessed 26/10/18. http://www.pharmatimes.com/news/vertex_mulls_over_nhs_englands_offer_for_cf_drugs_1244658.
10. FirstWord Pharma. 2018. 'Vertex Pharmaceuticals statement on position regarding talks with NICE over cystic fibrosis treatment Symkevi', Accessed 26/10/18. http://www.firstwordpharma.com/print/1584575?tsid=17.
11. Pharmaphorum. 2018. 'CF patients furious as Vertex turns back on NICE', Accessed 26/10/18. https://www.printfriendly.com/p/g/PxHd6f.
12. Selina McKee. 2018. 'MPs call on government to help with Orkambi debate', http://www.pharmatimes.com/news/mps_call_on_government_to_help_with_orkambi_debate_1228392.

SIRIUS MARKET ACCESS