NICE Appraisal Consultation Document (ACD) - Cystic fibrosis - lumacaftor and ivacaftor [ID786]

Cystic Fibrosis Trust consultation response – April 2016

Overview

The Cystic Fibrosis Trust (the Trust) is profoundly disappointed that NICE proposes not to recommend lumacaftor-ivacaftor therapy (Orkambi®) for routine use in the NHS in England.

This is a distressing announcement for the thousands of families who could benefit from the therapy that NICE's Appraisal Consultation Document (ACD) concludes is **a valuable new therapy for managing cystic fibrosis that has wider benefits to society, for people with cystic fibrosis, and carers of people with cystic fibrosis**.

Orkambi® may have a significant protective effect against future health deterioration for eligible individuals with cystic fibrosis. However, the evidence from the clinical trials and rollover studies to see if the therapy slows disease progression and facilitates compound health improvement is immature and, naturally, a confident assessment of the ultimate value it could bring is uncertain.

The ACD centres on concerns relating to:

- **Uncertainty** regarding longitudinal effects
- **Uncertainty** regarding clinical significance of acute effects
- **Uncertainty** regarding elements of economic modelling
- **Uncertainty** regarding transferability of clinical trial results to routine use

The Trust accepts that the NHS must use its resources carefully to deliver high-quality care for all.

However, it is imperative that it is now recognised that risk associated with making life-changing decisions on the use of new rare-disease medicines in the NHS where such degrees of uncertainty exist is unacceptable.

In the case of Orkambi®, this uncertainty persists in spite of the fact that the data used to assess the therapy was drawn from the largest ever clinical trial of a new cystic fibrosis medicine.

NICE and the Government must now accept that actively engaging to address uncertainty in modelling the long-term impact of medicines for chronic, rare diseases is the only viable option if a future of disease-modifying and more personalised interventions is to be realised.

Throughout the NICE scoping and appraisal process for this therapy, the Cystic Fibrosis Trust has highlighted the potential of the UK Cystic Fibrosis (CF) Registry to support reimbursement decision-

making for new cystic fibrosis therapies that are proven to be safe and effective, and boost the NHS's ability to confidently invest in new technologies.

In the Trust's submission to the NICE STA process, it was stated that:

> [Orkambi®] is a typical rare disease product in that it targets a small population with significant unmet need, has an innovative mechanism of action, and has an immature body of data that naturally cannot describe the full-extent of the clinical potential of this novel and innovative therapy.
>
> However, the product has sufficiently demonstrated safety and efficacy through well-powered and executed Phase III clinical trials. As such, the Cystic Fibrosis Trust believes that clinicians should be given the opportunity to prescribe this treatment with minimum delay.
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> Given the opportunities that present themselves in cystic fibrosis care – a defined patient population, a high-quality patient data registry, and a well-established network of specialist care centres with well-established protocols and routines for data collection – it is imperative that the Appraisal Committee explore how these assets can be innovatively used, within the assessment process, by all parties, to support negotiated access to this safe and effective therapy and to facilitate improved understanding of the therapy.

A copy of the principles of for using UK CF Registry data to support reimbursement decision-making, co-designed and agreed in principle by members of the CF specialist clinical community, representatives of the company, and representatives of CF services for NHS England, has been submitted alongside this response.

Solution

The UK CF Registry is a national, centralised web-based database that collects demographic, health and treatment data from consenting people with cystic fibrosis from every CF care centre in England, Wales, Scotland and Northern Ireland. The UK CF Registry is sponsored and managed by the Cystic Fibrosis Trust.

The infrastructure to undertake an assessment of the therapy's real-world impact across the whole eligible population in the UK already exists and, by embracing such a solution, the NHS would be able to develop its own extended and novel evidence base via the UK CF Registry's patient records, to confidently address uncertainty in the data set currently at its disposal and make a more confident valuation of the clinical and cost-effectiveness of the therapy.

The Trust firmly believes this solution is a progressive model for all new technologies for people with cystic fibrosis enabling access to safe, effective and innovative products faster, whilst providing the NHS with the robust, real world data to confidently support investment opportunities. For Orkambi®, we have witnessed the inevitable and agonising delay in access that is a consequence of the current approach to health technology appraisal for cystic fibrosis technologies.

It has been nearly a year since Orkambi® received marketing authorisation in Europe. People with cystic fibrosis who are eligible for the treatment within its marketing authorisation have now waited for over 22 months since the publication of the pivotal Phase III trials that demonstrated the treatment's clinical efficacy.

Critique of the Appraisal Consultation Document (ACD)

- **Disease severity**

The Trust is concerned that, despite the input of consultees, stakeholders and expert opinion the ACD presents a view of cystic fibrosis which is not consistent with the reality of the condition, its progressive nature, and its geno- and phenotypic expression.

Section	ACD extract
3.19	The ERG stated that because both trials included people with mild to moderate cystic fibrosis (that is, ppFEV1 of 40–90% at screening), the clinical evidence may not be generalisable to people with severe cystic fibrosis, or people with very mild cystic fibrosis.

Section 3.19 of the ACD refers to testimony from the Evidence Review group that describes mild, moderate and severe cystic fibrosis as definable by the measure of an individual's ppFEV1.

It should be made clear that, ultimately, cystic fibrosis disease severity depends on the type of mutations present and well as other modifying environmental and physiological factors. It is important that disease severity is not confused with acute health status.

- **Long term data uncertainty**

Section	ACD extract
3.23	The ERG noted that because the company's trials were short, the long-term effects of lumacaftor–ivacaftor were uncertain.
4.6	The committee recognised that longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis. However, it concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant.
4.7	The committee heard from the clinical experts that pulmonary exacerbations are associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant.

Section 3.23 of the ACD acknowledges the ERG's conclusion that all long-term effects of the therapy are uncertain.

Section 4.6 demonstrates the committee's acknowledgement of the primacy of the importance of longitudinal change over acute change in ppFEV1. However, it must be more clearly recognised that cystic fibrosis is a progressive condition, where long-term maintenance of ppFEV1 is an important clinical achievement, given the measure's well-established relationship with long-term survivorship. The conclusion associated with Section 4.6 – that acute improvements in ppFEV1 are modest and unlikely to be clinically significant – appears to dismiss the concept of ppFEV1 maintenance as a positive clinical outcome, and appears to disregard the evidence provided by clinical and patient experts, recorded in Section 4.13, that, in converse, an annual decline in ppFEV1 of ≥2% is treated as a reflection of rapidly declining lung function. The Trust seeks the committee's comment on these points.

In Section 4.7 the committee acknowledges the significance of the therapy's impact on hospitalisation. This fundamental aspect of the positive benefit described by trial data, with reduction in pulmonary exacerbations, indicates the potential for this treatment to slow the disease's progression versus Standard of Care in the long-term. This data is given disproportionately low standing in the ACD and the Trust seeks the committee's reassurance that its relationship to health maintenance is well represented in the documentation.

Section	ACD extract
4.11	The committee concluded that, overall, the company's methods for estimating survival seemed valid but there was uncertainty about how the differences in outcomes between the whole cystic fibrosis population and the population with the F508del mutation would affect the cost-effectiveness results.
4.12	The committee highlighted that there was also considerable uncertainty associated with how the company modelled the decline in ppFEV1 after 24 weeks.
4.12	The committee commented that because extrapolations for ppFEV1 decline were based on different, non-randomised studies for each treatment group, it would have been appropriate for the company to explore the impact on the ICER using the ppFEV1 decline for standard of care alone based on the 24-week trial data. The committee concluded that the company's methods for estimating changes in ppFEV1 were associated with considerable uncertainty and were likely to have overestimated the benefits of lumacaftor–ivacaftor treatment.
4.15	Therefore, it concluded that there was uncertainty associated with the treatment effect on BMI in the company's model
4.20	The committee concluded that people could discontinue lumacaftor– ivacaftor after 24 weeks, but the rate of discontinuation was uncertain.

Addressing the comment in Section 4.11, in order to confidently estimate survival in the relevant population, supportive data is available to both NICE and the company upon request from the UK CF Registry.

Sections 4.12, 4.15 and 4.20 highlight the difficulty of estimating performance beyond the 24-week trial period and the Trust, again, indicates the potential of the UK CF Registry to explore and overcome this uncertainty using real-world evidence.

4.24	The committee acknowledged that the company had used the data from its trials when available, which were recognised as the largest trials in cystic fibrosis to date.
4.24	The committee also agreed that there was considerable uncertainty around: • the estimates of relative effectiveness for ppFEV1 decline • the rapid rate of ppFEV1 decline in the standard of care group • how the treatment effect was modelled when people came off treatment and over the longer term (that is, no waning effect of treatment over time) • how independent the effects of lumacaftor–ivacaftor on ppFEV1 and on pulmonary exacerbations were • potential double counting of cost savings associated with hospitalisations and • The company's utility estimates.

Section 4.24 outlines areas of **considerable uncertainty** whilst simultaneously acknowledging the scale of the trials used to source the novel data used to describe this treatment effect.

It must be acknowledged that the Single Technology Appraisal of Orkambi® has failed to produce an unequivocal recommendation, in the respect that, with or without the committee's preferred assumptions, the inherent uncertainty regarding the therapy's long-term performance leave the committee's conclusions begging more questions than are answered.

- **Concluding remarks**

In Section 6.1 of the ACD, NICE proposes to review the guidance issued 3 years from the publication of this guidance.

This timescale in unconscionable, whilst an alternative option exists. The Trust firmly believes that NICE, the NHS and Government must work cooperatively, alongside the company to address the challenge of

The Trust welcomes the committee's comment on the Trust's document describing the principles of using the data collected by the UK CF Registry to collect real world evidence supporting clinical- and cost-effectiveness assessments.