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15 January 2019

Dr Sarah Wollaston MP
Chair
Health and Social Care Committee
House of Commons
London
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Dear Dr Wollaston,

I am writing in relation to your inquiry into drugs which may potentially provide patient benefit but where their pricing means they are not considered cost effective, and, therefore, a good use of NHS or taxpayer resources.

As you know, we have a held a number of meetings with Vertex to provide clarification about aspects of appraisal methodology. We have already provided you with the letters we sent to the company following these meetings. We met Vertex again on 30 November, following which we sent a third clarification letter, a copy of which is enclosed.

We have also reviewed the submission made to the Committee by Vertex and we thought you might find it helpful to be aware of some comments we have on their submission, particularly in the memorandum and appendix 3b.

Clinical data

In the memorandum[1], Vertex notes that '*There is currently no cure for CF and the median age of survival for people with CF in the UK is 31*'. Our reading of the economic model[2] submitted to us by Vertex is that they used a projected median of 41 years, based on an analysis of the UK CF Registry.

Vertex suggests[3] that '*since Kalydeco was made available to NHS patients in 2013, data from the UK registry shows that it has been associated with a mortality relative*

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[1] Memorandum: page 1, 4th bullet under the first heading
[2] Vertex's economic model; dated 110116, 'mortality worksheet'
[3] Memorandum: page 2, 2nd bullet under the second heading

risk reduction of 53%, hospitalisations for pulmonary exacerbation reduction of 43%, and pulmonary exacerbations risk reduction of 42%'.

We note that the most recent report[4] on the registry data presents the relative risk reduction for mortality in the UK cohort as 48%, and not statistically significant. The same report also notes that because of differences in the genetic make-up of patients treated with Kalydeco and with comparators, there is a question as to whether the survival differences already existed between these two populations before the availability of Kalydeco.

In the same memorandum Vertex notes that '*In addition to providing acute improvements in lung function, Orkambi significantly reduces the annual rate of lung function decline by 42%, a degree of benefit similar to that observed with Kalydeco (a 47% in lung function decline)*'.

This estimate of the reduction in lung function decline comes from a recent publication[5] of the extension study (PROGRESS) of the two pivotal trials (TRANSPORT and TRAFFIC). In this study, patients who were on Orkambi as part of the pivotal trials continued with treatment, and patients who had been receiving a placebo were offered Orkambi. Lung function decline experienced by both groups was compared with a 'matched cohort' from a registry. This outcome is therefore not the result of a randomised, double-blind, comparison.

Economic data

Vertex suggests in its memorandum[6] that '*NICE only values Orkambi as having a value of £10,300/year, despite the fact that is has a projected survival benefit of 23 years*'.

We have not suggested that Orkambi has a value of £10,300/year; we do not express the value of new drugs in this way. We use the cost per quality adjusted life year as an expression of the cost effectiveness of a new drug. Our estimates of the cost effectiveness of Orkambi are contained in our submission. The figure of £10,300/year is an estimate of an annual cost per patient treated with Orkambi, taken from the offer made to Vertex by NHS England. Vertex also refer to a projected survival benefit of 23 years for a cohort of patients that are 2 years old. We have not seen any data to support this. The economic base case put forward by Vertex reported an improvement in projected median survival of 7.69 years and an increase in the mean residual life expectancy (undiscounted life-years gained) of

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[4] https://thorax.bmj.com/content/73/8/731

[5] https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(16)30427-1/fulltext

[6] Memorandum: page 3, 5th bullet under first heading

9.42 years, using a patient cohort with a mean age of 25.5, reflecting the two pivotal trials[7].

NICE's methodology

In both the memorandum and appendix[8] Vertex suggests that '*While NICE's Single Technology Appraisal (STA) methodology works for many medicines and diseases, it requires modernisation to appropriately assess medications that treat rare or orphan diseases, including our disease-modifying CF medicines*'.

We do not agree with this. Of the 48 topics with European Medicines Agency 'orphan status' that we have so far appraised, 75% have received a positive recommendation.

Yours sincerely,

Sir Andrew Dillon
Chief executive

Enc. Third clarification letter to Vertex, 13 December 2018

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[7] Evidence submission Vertex 2016: page 123 of 150, and page 83 of 150 [https://www.nice.org.uk/guidance/ta398/documents/committee-papers]

[8] Memorandum: page 3, 3rd bullet under first heading / Appendix 3b: 1st bullet point