NICE Health Technology Appraisal
On

Colistimethate Sodium and Tobramycin Dry Powders for inhalation for treating pseudomonas lung infection in Cystic Fibrosis.

TO: NICE	FROM: Healthcare Improvement Scotland 13 November 2012

Comments provided to Healthcare Improvement Scotland by: [redacted]

The response below takes into account three areas – my role as an invited respondent to the EUCERD (EU Committee of experts in Rare Diseases), someone who has cared for adults and children with CF and as a basic scientist in CF.

Clinical need and practice section 2.1

The statements in this section although technically correct, have recently been extended to include multiple additional mechanisms that are unrelated to CF as an Ion Transport Disease (ITD). It is important to add that Cystic Fibrosis is also recognised to be a disorder of pathogen sensing and a disorder of cell stress and hyper-inflammation.

Section 2.2

1 in 64 people in the United Kingdom who have Cystic Fibrosis are of Asian origin (McCormick et al Eur J Human Genetics) . In addition, increased inter marriage between races is complicating the 'CF as an ITD of whites in Europe' accepted clinical picture. The statement it is much less common in people of African and Caribbean and Asian origin should be removed and replaced with an appropriate statistic.

The last paragraph is misleading as it mixes two unrelated issues. The 103 deaths of UK patients with a median age of 29 has advanced by approximately seven years since the year 2000. *This median age at death is reflective of care using older therapies and prior to screening that occurred some twenty years ago.*

It is imperative not to mix this issue up with median survival which for current cohorts, cannot be predicted. For example it is expected that less than 5% of babies diagnosed with Cystic Fibrosis today will die before their 20th birthday.

Section 2.3

Childhood CF and adult CF differ such that hypertonic saline is not of benefit in childhood.

And whilst the statements in section 2.3 are technically correct, it is also important to note that nutrition is one of the major idrivers that relates to pulmonary health in Cystic Fibrosis up to a max BMI (Kastner-Cole et al J Cyst Fibrosis).

Section 2.4

The idea that single organisms can be thought of in isolation as pathogenic factors in Cystic Fibrosis, whilst technically true, is not reflective of modern understanding of the condition. The complex microbiology of Cystic Fibrosis is now out of date as it does not include the most crucial understanding that the pseudomonas is stimulated to grow by factors secreted by other pathogens. The words complex micro-biome are key. For example, the role of viruses such as Rhinovirus which persists in Cystic Fibrosis lungs for unknown reasons should be remembered.

Section 2.5

A comment might be added that host factors which vary between patients even with the same genotype in Cystic Fibrosis seem to be important in the transition from no infection through to long term sustained infection (Corvol et al J Cystic Fibrosis)

Section 4.1.2

Whilst I can see the use of throat irritation as a complication or side effect of the treatment whether it is with the agent in question or with another dry powder formulation, when a patient coughs it is rather more difficult to be sure that this is actually a side effect. After all should the bacteria be killed and more mucus production and/or a different quality of mucus is produced, the patient may cough in order to clear the mucus from the lung.

Section 4.1.3 and Section 4.1.4 in combination.

The work of Taylor-Robinson shows that the intrinsic variability in a given patient in their lung function due to the condition is 5% (random error) so I fail to see how the statement in section 4.1.4 can be supported. There is no difference between the two treatments in my view.

Section 4.1.5

My comments above apply in that we don't know whether the so called acute exacerbation is actually a benefit of treatment in this condition.

Section 4.1.6

Is it necessary to use dysgeusia? 70% of 'taste' is actually smell!

Section 4.1.7

Given the nature of the condition I could not really understand why quality of life criteria would be of any benefit in this kind of treatment.

Combining Sections 4.1.8 and 4.1.9.

From my perspective given that the rate of decline of lung function is approximately 1% per year (or less) and that the variability in the measure of lung function is around 5% just as a random variation, it seems that such

studies are never going to reveal any interesting results without much larger numbers and better stratification.

Section 4.1.10.

It is commonly observed that the complex microbiome of the Cystic Fibrosis lung means that resistance that is reported to one particular antibiotic bears no relationship to the clinical outcome which, despite 'resistance' is nonetheless associated with an improvement of lung function and a better weight for the patient. Indeed it is commonly observed that one of the earliest indications of being ill in Cystic Fibrosis is a drop in the weight percentile.

Section 4.1.14.

I concur with these conclusions and would suggest that any future evaluations should include a prior assessment using registry data of the number and frequency of outcome related events. This should be readily available given the quality and density of data this is now stored on the registries. New data are available (Boelle et al Orphanet web site, J Rare Disease) on the CF centiles for lung function.

Section 4.2.10.

This is a critically important section because it reflects the fact that the state of the Cystic Fibrosis patients, particularly those born after 1986 when proper nutritional therapy became available, is very different from those born before this date who had an early childhood experience of poor growth and poor body mass index. This impacts on lung development.

I note that the assessment group did not include a switch between the two different agents and this is an important clinical parameter because patients do change as a result of the development of allergies having been on certain treatments for a long period of time. The clinician is then faced with either trying to desensitise the patient or switching therapy.