Respiratory Subcommittee of PTAC
Meeting held 30 April 2014

(minutes for web publishing)

Respiratory Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note:

- that this document is not necessarily a complete record of the Respiratory Subcommittee meeting; only the relevant portions of the minutes relating to Respiratory Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Respiratory Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 14 & 15 August 2014, the record of which will be available in October 2014.

Record of the Respiratory Subcommittee of PTAC meeting held at PHARMAC on 30 April 2014

1 Ivacaftor application for funding

Application

1.1 The Subcommittee considered an application from Vertex Pharmaceuticals (Australia) Pty Ltd for the listing of ivacaftor on the Pharmaceutical Schedule for the treatment of patients with cystic fibrosis.

Recommendation

1.2 The Subcommittee deferred making a recommendation until data is available from the clinical trials evaluating ivacaftor in combination with lumacaftor (VX-809) and until PHARMAC has completed further cost utility and budget analysis on three discrete groups of patients – those who are early in the disease course, as a bridge to transplant and patients who are in the late stages of the disease.

Discussion

1.3 The Subcommittee noted that cystic fibrosis (CF) is caused by a genetic defect of a chloride channel regulator (the cystic fibrosis transmembrane conductance regulator or CFTR) resulting in the dehydration of secretions which leads to sticky viscous secretions. Members noted that there are more than 1600 CFTR gene mutations and a wide spectrum of disease severity that cannot necessarily be predicted from genotype. Members noted that approximately 4% of CF patients worldwide have the Class III (gating) mutation, G551D on at least one allele. This type of mutation results in a CFTR protein that is present in the apical cell membrane but displays greatly reduced chloride transport. The Subcommittee noted that ~26 of the 430 cystic fibrosis patients in New Zealand have the G551-D gene.

1.4 The Subcommittee noted ivacaftor is a CFTR potentiator which increases chloride channel function by facilitating CFTR opening. Members noted that ivacaftor is registered for use in New Zealand for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene with a recommended dose of 150 mg taken orally every 12 hours with a fat containing snack or meal. The Subcommittee noted there were two main double blind randomised trials – STRIVE (Ramsey et al NEJM 2011; 365:1663-72) and ENVISION (Davies et al Am J Respir Crit Care Med 2013;187, 11:1219-1225).

1.5 The Subcommittee noted that of the 161 patients over the age of 12 years enrolled in the STRIVE study, 83 were randomised to ivacaftor, 78 to placebo and patients were treated for 48 weeks. The primary endpoint showed a 10.6% increase in absolute predicted FEV_1 with treatment compared with placebo

(P<0.0001), improvement was seen by day 15 and maintained through week 48. There was a reduction in exacerbations (47 vs 99), hospitalisations (21 vs 31), days in hospital for exacerbations (3.9 vs 4.2) an increase in the scores in the CFQ-R compared with a decrease of 2.7 points in the placebo group and improved weight gain (3.1 kg vs 0.4 kg). The incidence of adverse events through week 48 was similar in the two groups. The ivacaftor group had a higher level of adverse events leading to interruption but not discontinuation of the drug than placebo (13% vs 6%). More placebo patients discontinued treatment than those on ivacaftor (5% vs 1%). The Subcommittee noted that 70% of patients in this study were also on dornase alfa.

1.6 The Subcommittee noted 52 children aged between 6 and 12 were enrolled in the EVISION study and were evenly divided between ivacaftor and placebo. Again, the primary endpoint was the absolute change from baseline through week 24 in the percent of predicted FEV_1. An improvement was seen by day 15, by week 24 there was an absolute improvement of 12.6 percentage points compared to 0.1% in placebo and 10.7% vs 0.7% at week 48. Further benefits were an increase of 3.7 kg in the ivacaftor group vs 1.8 kg, an increase in the CFQ-R score of 6.3 points vs 0.3 points and a significant drop in sweat chloride concentrations. Exacerbations were not significantly different between the two groups and the adverse events were similar.

1.7 The Subcommittee noted a randomised, double-blind placebo-controlled phase 2 crossover study conducted by Davies et al (Lancet Respir Med 2013;1: 630-638). The study enrolled 21 patients of whom 20 patients received treatment and 17 completed the trial. The planned primary outcome was a change in the lung clearance index (LCI) of which there was a significant difference between the ivacaftor treatments and placebo (p=0.0001). There was a significant difference in the FEV_1 measurements for the two treatments (p=0.0103) but not in the CFQ-R scores.

1.8 The Subcommittee noted that the DISCOVER study (Flume et al Chest.2012; 142(3):718-724 was a 16 week safety study sponsored by the company but not designed by the company. There were 112 patients enrolled in the ivacaftor arm and 28 in the placebo arm. The primary endpoint was evaluated by assessment of adverse events, clinical laboratory values, ECGs, vital signs and physical examinations. No serious adverse events occurred.

1.9 The Subcommittee noted three patient studies – Hebestreit et al. J Cyst Fibrosis 2013;12: 599-603, Wood et al Respirology Case Reports 2013;1(2):52-54 and Barry et al Poster, Cystic Fibrosis Conference. All three reported on patients with severe disease treated with ivacaftor in clinical settings either under compassionate grounds or named patient programs.

1.10 The Subcommittee noted the dose defining study by Accurso et al study (Study 101, NEJM 2010). Four patients in four groups received either 25 mg twice daily (BD), 50 mg BD, 75 mg BD or 150 mg BD and four patients received placebo. The reduction in FEV_1 percentage of predicted between the 75 mg BD and 150 mg BD treatment regimens was similar (10.0% and 10.5% respectively). The decision to proceed with the 150 mg BD protocol and stop using the 75 mg BD is not well explained. The results suggested that 75 mg BD may work just as well

as the 150 mg BD recommendation which would reduce the cost of the treatment.

1.11 The Subcommittee noted that only approximately 90 of the 430 patients in New Zealand who have been diagnosed with cystic fibrosis are taking dornase alfa. The Subcommittee noted that, outside of the main centres, there is a lack of multidisciplinary teams to treat cystic fibrosis patients which could have a detrimental effect on patients' treatment. Members noted that in general patients in New Zealand are sicker than their counterparts in the UK and US where patients have easier access to multidisciplinary teams.

1.12 The Subcommittee noted that ivacaftor represented a significant improvement in the treatment of cystic fibrosis which is a high need area and if cost were not an issue then they would recommend funding this drug. The Subcommittee noted that ivacaftor it is a unique product that could be highly beneficial but noted that that there were still a lot of unknowns. The subcommittee noted that there may be novel ways that it might be used, for example in short bursts in the treatment of children. Members noted that while this is a unique product it is not a cure. Members noted that ivacaftor would be given in combination with all treatments patients are currently taking.

1.13 The Subcommittee noted that cystic fibrosis is a chronic condition and to date follow-up has only been to approximately three years. The effect of ivacaftor beyond this time frame is unknown. However, following the improvement in a patient's FEV_1 of ~10.5% as seen in the clinical trials, the Subcommittee considered that it would not be unreasonable to expect that FEV_1 would slowly decline in a similar way to a patient with non-cystic fibrosis bronchiectasis.

1.14 The Subcommittee noted that only patients with the G551-D-CFTR mutation gene would benefit from ivacaftor although members noted that the FDA had recently extended the licence in the US to cover eight additional mutations G178R, G551S, S549N, S549R, G1244E, G1349D, S1251N, S1255P. It is estimated that the expansion to these mutations would make little difference to the numbers of patients eligible for treatment as these subgroups are very rare. Members noted that it is common practice to do CFTR gene mutation analysis in New Zealand.

1.15 The Subcommittee noted there would be a significant financial impact in listing ivacaftor at the current price of ~$900.00 per day which would equate to ~$8 million per year for 26 patients. Members noted that results from two new phase III trials (TRACTOR and TRANSPORT) studying ivacaftor in conjunction with Vertex's new product lumacaftor in patients homozygous for the F508del mutation are expected later this year. Members noted that if the results of these two trials are positive there would be a significant financial risk to the Pharmaceutical Budget. The F508del mutation is the most common mutation of the CFTR gene opening treatment to ~75% of the CF population in New Zealand.

1.16 The Subcommittee deferred making a recommendation at this stage pending further analysis by PHARMAC. To help clarify on which patient populations may benefit most, the Subcommittee have asked for cost utility and budget analysis around three discreet groups of patients – those in the early stage of the disease,

those with moderate disease already showing decline in FEV1 (similar to the initial targeting of dornase alfa) and those with severe disease requiring a bridge to transplant. The Subcommittee also wanted further information on the results of the trials with lumacaftor and in the long term use of ivacaftor from the ongoing trials.

2 Tobramycin inhalation solution (TOBI) and tobramycin powder for inhalation (TOBI Podhaler) for the treatment of *Pseudomonas Aeruoginosa* infections in patients with cystic fibrosis

Application

2.1 The Subcommittee considered an application from the supplier, Novartis New Zealand Limited, for consideration of funding for tobramycin inhalation solution (TOBI) and tobramycin powder for inhalation (TOBI Podhaler) for the treatment of Pseudomonas Aeruginosa infections in patients with cystic fibrosis

Recommendation

2.2 The Subcommittee **recommended** funding both TOBI and TOBI Podhaler under the current access restriction (endorsement) if cost neutral to the tobramycin IV preparation at a dose of 160 mg twice daily.

2.3 The Subcommittee **recommended** funding both TOBI and TOBI Podhaler with a medium priority under Special Authority for patients who have a reaction to the IV tobramycin.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

2.4 The Subcommittee noted the application from Novartis for funding of TOBI and the TOBI Podhaler. Members noted that the current standard of care was to use IV tobramycin in a nebuliser at a dose of 160 mg or 320 mg daily in divided doses. Members noted that there was a weaker level of evidence for use of IV tobramycin compared to the use of TOBI but it had been standard of care in New Zealand since the 1990s due to the lack of alternatives. The Subcommittee considered that the comparator for TOBI and TOBI Podhaler would be IV tobramycin at a dose of 160 mg twice daily.

2.5 The Subcommittee noted that the use of nebulised colistin sulphomethate was much less frequent in New Zealand compared to the UK, despite the availability

of a solution licensed for nebulisation. It was noted that the evidence to support the use of nebulised colistin sulphomethate was also limited and overall the Subcommittee concluded that nebulised colistin sulphomethate was therefore not an appropriate price comparator. The Subcommittee further noted that the price differential between colistin sulphomethate and that proposed for TOBI was small.

2.6 The Subcommittee noted that many IV tobramycin preparations contain preservatives and have a pH level that was not ideal for nebulisation as it could potentially cause bronchospasm or long-term loss of lung function. Members noted that for patients who were irritated by the IV solution a dose of salbutamol could be given prior to nebulisation to reduce bronchospasm.

2.7 The Subcommittee noted that the supplier's evidence for both the TOBI and TOBI Podhaler compared these products against placebo. Members noted that the studies showed a statistically significant improvement in FEV_1 and a reduction in hospitalisation compared to placebo. Members noted that the studies also show that both formulations of TOBI reduced the *pseudomonas aeruginosa* density in patients and there were fewer IV antipseudomonal antibodies.

2.8 The Subcommittee noted the Nikolaizik et al study (Can Respir J. 2008: 15 (5): 259-62) an open crossover study comparing 80 mg tobramycin IV with TOBI 300 mg twice daily. The Subcommittee noted that while the variability in responses was large there was no statistical difference between the two groups in FEV_1.

2.9 The Subcommittee noted that resistance can develop as a result of inhalation of tobramycin, however this appeared to be reduced with use of the 28 day on and 28 day off cycle.

2.10 The Subcommittee noted that the TOBI Podhaler would be a more convenient presentation for cystic fibrosis (CF) patients who required tobramycin. Members noted that it would reduce the time required for a patient to receive their antibiotics. Members noted that CF patients often were on a complex regimen of pharmaceuticals and non-pharmaceutical interventions (i.e. physiotherapy) and reducing this would help the population.

2.11 The Subcommittee noted that both forms of TOBI were more effective than placebo but probably no more effective than IV tobramycin. Members noted that IV tobramycin was an off-label usage of the product and both presentations of TOBI were registered for use in CF patients with *pseudomonas aeruginosa.* Members considered that for the majority of CF patients there would be no additional clinical benefit from TOBI or TOBI Podhaler and recommended they be listed only if cost neutral to IV tobramcyin.

2.12 The Subcommittee considered that for those patients who experience significant bronchospasm following IV tobramycin diagnosed by spirometer that either presentation of TOBI would provide a benefit. Members considered that either presentation could be funded under a Special Authority for this patient population with a medium priority.

3 Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis

Application

3.1 The Subcommittee considered an application from a clinician, for consideration of funding of azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis.

Recommendation

3.2 The Subcommittee **recommended** funding of azithromycin for the prevention of exacerbations in non-cystic fibrosis bronchiectasis patients who have previously had at least three exacerbations in the past 12 months with a medium priority.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

3.3 The Subcommittee noted the application from a clinician for funding of azithromycin for patients with non-cystic fibrosis (CF) bronchiectasis.

3.4 The Subcommittee noted the minute from the Anti-Infective Subcommittee which noted that erythromycin ethyl succinate was funded without restriction and could be used in patients for this indication. The Anti-infective Subcommittee noted that evidence supporting one macrolide over another at this time is still incomplete and considered it was not clear at this stage what treatment duration or macrolide dosage or which group may get most benefit (for example young children, older adults, number of exacerbations >3 in prior 6 months). The Anti-Infective Subcommittee recommended presenting a paper to the Respiratory Subcommittee of PTAC regarding the use of macrolides in this paediatric and adult bronchiectasis patient population.

3.5 The Subcommittee noted the papers that the Anti-Infective Subcommittee reviewed and considered that the Anti-Infective Subcommittee's summary of the results was consistent with members' interpretation of the papers. The Subcommittee considered that the trial for erythromycin for exacerbations in non-cystic fibrosis bronchiectasis did not compare well with the azithromycin studies due to the size of the relative patient populations.

3.6 The Subcommittee noted that they were not aware of any other clinical papers regarding the use of macrolides for preventing exacerbations in non-cystic fibrosis bronchiectasis.

3.7 The Subcommittee noted that Maori and Pacific Island children have significantly higher rates of non-cystic fibrosis bronchiectasis than the general population.

3.8 The Subcommittee considered that azithromycin had benefits over erythromycin in dosing frequency and less gastric side effects. The Subcommittee noted that Valery et al trial (Lancet Respir Med. 2013; 1:610-20) used directly observed therapy (DOT) in the NZ arm of the study and that once weekly azithromycin would allow this to occur. Members noted that DOT would not be feasible for the entire bronchiectasis patient population but in certain cases it may be appropriate.

3.9 The Subcommittee noted that while the mechanism of action of long-term azithromycin was unclear it was in part being prescribed for its anti-inflammatory properties rather than as an antibiotic in this patient population. Members noted that ad-hoc analysis of the use of macrolides in the patient population studies showed a reduction in other infections, particularly skin and soft tissue infections. Members considered that this patient population was already over represented in cases of hospitalisation of these infections and this treatment may provide an additional health benefit.

3.10 The Subcommittee noted that prior to initiating a patient on azithromycin the patients with known risk factors for QT prolongation, such as concurrent dosing of medications which prolong the QT interval, should be given a baseline ECG and should have negative cultures for non-tuberculous mycobacteria. Members considered that if azithromycin was available then it should be for all patients not just those colonised with pseudomonas.

3.11 The Subcommittee noted that there was the potential for resistance to develop as a result of long term macrolide use and this could be a significant issue in the patient population being treated.

3.12 The Subcommittee **recommended** funding of azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis with a medium priority. The Subcommittee noted that there was no consistent evidence as to the appropriate dosing regimen for azithromycin but once weekly or three times weekly appeared to be similarly effective.

3.13 Members noted that azithromycin had recently had a widening of access and considered that this should be reviewed as azithromycin was an important antibiotic and should be maintained for specific populations. Members **recommended** that azithromycin should be restricted to both CF and non-CF bronchiectasis, treatment of chlamydia trachomatis, prophylaxis and treatment of young children for pertussis and some other inflammatory lung disease such as bronchiolitis obliterans syndrome.