Respiratory Subcommittee of PTAC
Meeting held 24 May 2013

(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 1 & 2 August 2013,the record of which will be available in October 2013.

Regarding item 4, the Committee noted that the application to list omalizumab had previously (2007) been recommended for decline by the Subcommittee and PTAC. The Committee noted that the Respiratory Subcommittee had reviewed an updated application from the supplier and had now recommended listing with a medium priority. The Committee considered that, due to the cost of treatment with omalizumab, it would need to review the data before making a recommendation.

Record of the Respiratory Subcommittee of PTAC meeting held at PHARMAC on 24 May 2013

1 Previous recommendations/action points

1.1 The Subcommittee noted that all action points recommended at the February 2012 meeting had been completed or was in the process of being completed except the educational program which is yet to be started.

2 Hospital Medicines

2.1 The Subcommittee noted that from July this year, PHARMAC will take over responsibility for making decisions on the funding of pharmaceuticals for use in DHB hospitals, and this expanded responsibility will extend to PTAC and its subcommittees. The Subcommittee noted that a nationally-consistent list of medicines that will be available in all DHB hospitals will be published in the Pharmaceutical Schedule (section H) and, as with the community section of the Schedule, will be updated on a monthly basis.

2.2 The Subcommittee noted that some hospital pharmaceuticals will have prescribing restrictions on their use, either in the form of prescriber-based restrictions or restricted indications (or, in some cases, both). These restrictions would apply nationally. The Subcommittee noted that, prescriber level restrictions are being used sparingly, given that not all DHB hospitals have representatives of all specialities available on staff, and obtaining recommendations from clinicians in other hospitals can be time-consuming.

2.3 The Subcommittee noted that for pharmaceuticals with a prescriber restriction, any clinician will be able to prescribe the pharmaceuticals either under a protocol approved by the DHB hospital or by recommendation from a clinician of the type stipulated in the restriction. The Subcommittee noted that, using protocols and/or guidelines, DHB hospitals would be able to overlay their own prescriber-level restrictions on top of any national restrictions, to account for their particular staffing constraints.

2.4 The Subcommittee noted concern that a number of antibiotics routinely prescribed by Respiratory Physicians for the treatment of cystic fibrosis (and bronchiectasis) patients are being restricted to Infectious Disease Physicians and Clinical Microbiologists and considered that access should be widened to Respiratory Physicians and Paediatricians. The Subcommittee noted that this was also the case for some antibiotics commonly used in the treatment of TB. The Subcommittee noted that protocols would need to be written for these products or, alternatively, treatment guidelines could be written for the disease state or follow the microbiology antibiotic sensitivities test for any particular bacteria. Members noted that in the future there would be a National Antibiotic Guideline.

2.5 The Subcommittee noted that PHARMAC are endeavouring to align restrictions in the hospital with restrictions in the community.

2.6 The Subcommittee noted PHARMAC's view that during the transition process it was important for DHB staff to feedback on any omissions or difficulties.

2.7 Members noted that therapies restricted in the community to cystic fibrosis should be widened to include bronchiectasis and that there is a high rate of bronchiectasis in New Zealand. Members considered it would be useful for PHARMAC to receive an application from clinicians in support of widening access of antibiotics in the community.

2.8 Members noted that the tem “internal medicine “ may be misinterpreted and should be replaced by the term “all internal medicine specialities”.

3 Therapeutic Group Review Update

3.1 The Subcommittee noted the review of funded respiratory pharmaceuticals provided by PHARMAC staff. The Subcommittee considered that there was no significant unmet need in this group. However, the Subcommittee noted that the educational program to be directed at doctors, nurses and their patients encouraging the proper use of inhalers and spacers has yet to commence, and the funding for this education program is essential due to the high level of non-compliance .

3.2 The Subcommittee noted the copy of the proposed respiratory and allergies therapeutic group section of the forthcoming Hospital Medicine List provided by PHARMAC

Inhaled short acting Beta-Adrenoceptor Agonists

3.3 Members noted that terbutaline turbuhaler is a useful product for school children due to the reluctance of children to use a spacer in the school environment.

3.4 Members noted that Ventolin continues to be the most dispensed salbutamol inhaler with ~65% of all dispensings being for Ventolin.

Inhaled Anticholinergic Agents

3.5 The Subcommittee noted that, in early 2012, some changes were made to the Special Authority criteria for tiotropium as a result of applications from the supplier, resulting in widened access.

3.6 The Subcommittee noted that there are some patients whose lung function has been preserved following treatment with tiotropium.

3.7 The Subcommittee discussed the changes that had been made in the GOLD classification of COPD and noted that the Special authority access criteria for tiotropium do not align with the new GOLD classifications. Members noted that the COPD Assessment Test (CAT) is now the gold standard when measuring patient’s symptom levels. Members considered that the access criteria should be aligned with the new GOLD classifications and CAT scores and should be focussed on the treatment of symptoms and prevention of exacerbations.

3.8 The Subcommittee considered that patients with two or more exacerbations in the previous year are at high risk of continuing to have exacerbations and would benefit from treatment with tiotropium.

3.9 The Subcommittee **recommended** amending the Special authority criteria for tiotropium by removing the FEV_1 requirement for the Special Authority, adding in a

criteria restricting access to those patient with established COPD and frequent exacerbations and including a symptom threshold with a high priority.

3.10 The Subcommittee noted that the biggest unmet need is in those patients who have frequent exacerbations and those on oral steroids.

Inhaled Corticosteroids

3.11 The Subcommittee noted that fluticasone dominates this market and that while the number of prescriptions written for inhaled corticosteroids has remained relatively steady over the past three or four years, the expenditure is decreasing.

Inhaled Long-Acting Beta-Adrenoceptor Agonists

3.12 The Subcommittee noted the significant decrease in the use of long acting beta-adrenoceptor agonists (LABAs) over the past 6 years and in particular since access was widened to the combination inhalers in February 2012.

3.13 Members noted that, at their February 2012 meeting, PTAC had reviewed an application from Novartis for listing indacaterol described as a once a day, ultra long-acting beta-adrenoceptor agonist for the treatment of COPD. The Subcommittee noted that PTAC had recommended indacaterol be listed on the Schedule at a price that is cost neutral to the currently listed LABAs.

3.14 The Subcommittee noted that indacaterol might result in a reduced use of tiotropium as there is some evidence that indacaterol is more effective than currently listed LABAs and the once daily dose may improve compliance. The Subcommittee noted that there were unlikely to be increased safety issues with indacaterol and the arrhythmia background rate has been shown to be the same as other LABAs.

Combination LABA/ICS inhalers

3.15 The Subcommittee noted the increase in prescriptions for combination over the past 6 years. Members also noted that the average doses of corticosteroids have continued to improve with the proportion of patients on 1000 mcg beclomethasone equivalents decreasing every year.

3.16 Members reviewed the current Special Authority criteria for combination LABA/ICS inhalers and considered that a fluticasone dose of 500mcg per day (or 800mcg of beclomethasone or budesonide) to be too high for children aged between 12 and 18 and considered the age should be changed from over 12 years of age to over the age of 18 years.

3.17 The Subcommittee noted that high dose fluticasone with salmeterol (Seretide) was considered by PTAC at its November 2010, February 2011 and August 2011 meetings. The Subcommittee agreed with PTAC, who were concerned about the high dose of corticosteroid in the combination product, and agreed with the recommendation to decline the application.

Dornase Alfa

3.18 The Subcommittee noted that access to dornase alfa had been widened to all cystic fibrosis patients with effect from 1 May 2012 supported by a PTAC recommendation. The noted that there had been an increase in use of dornase alfa

in the community since the widening of access but the number receiving treatment remains low at ~90 patients out of the 430 patients who would be eligible for trial.

3.19 The Subcommittee noted that, following consultation on listing respiratory products in the hospital medicines list, PHARMAC had received feedback that dornase alfa was used for the treatment of hospital inpatients in a number of therapeutic areas on a short term basis. These therapeutic areas included:

- Cystic fibrosis – chronic and acute use
- Chronic asthma
- Segmental/lobar collapse consolidation
- Bronchial casts
- Intensive care use –management of acute severe respiratory illnesses with persistent or significant atelectasis of several segments or lobes.

3.20 The Subcommittee reviewed the proposed restriction for the use of dornase alfa in a hospital setting and recommended the following changes to the proposed restrictions in Section H of the Pharmaceutical Schedule (changes in bold and strike through)

Dornase alfa
Nebuliser soln 2.5 mg per 2.5 ml ampoule

RESTRICTED
Cystic fibrosis
For use in patients with approval by the Cystic Fibrosis Advisory Panel

Significant mucous production ~~(excluding cystic fibrosis)~~ – Respiratory Physician, Intensivist or Paediatrician
Treatment period restricted to ~~two~~ **four** weeks where
Both:
a. Patient is an inpatient
b. The mucous production cannot be cleared by first line chest techniques

3.21 The Subcommittee noted that some patients require dornase alfa for bronchoscopy in an outpatient setting and considered that that indication would be covered by the recommended restriction as the procedure would be carried out in a day clinic. The Subcommittee noted that dornase alfa is used to treat mycobacterium avium complex and that access for this indication was through the NPPA pathway. The Subcommittee considered that it is appropriate to consider access to dornase alpha for indications outside of the above restriction (or the restriction to cystic fibrosis in the Community Schedule) via the NPPA pathway.

Leukotriene Receptor Antagonists

3.22 The Subcommittee noted the use of montelukast remains quite low and reviewed the current Special Authority criteria.

3.23 The Subcommittee considered that the Special Authority criteria for montelukast for patients with pre-school wheeze were appropriate.

3.24 The Subcommittee reviewed the Special Authority criteria for montelukast for patients with exercise-induced asthma. The Subcommittee considered that unstable patients should not be required to be currently treated with maximal asthma therapy including inhaled corticosteroids and long acting beta-adrenoreceptor agonists and recommended that the Special Authority criteria be amended accordingly.

3.25 The subcommittee considered that approximately 4% of children and 8% of adults have severe uncontrolled asthma and approximately half of these would meet the previous treatment with maximal asthma therapy requirement of an amended access criteria.

3.26 The Subcommittee recommended the following changes to the Special Authority criteria for exercise-induced asthma:

Both:

1 Patient ~~is being~~ ~~treated~~ **has been trialled** with maximal asthma therapy, including combination inhaled corticosteroids and long-acting beta-adrenoceptor agonists; and

2 Patient continues to receive optimal inhaled corticosteroid therapy; and

3 Patient continues to experience frequent episodes of ~~exercise-induced~~ bronchoconstriction.

Nasal Preparations (Allergy Prophylactics)

3.27 The Subcommittee reviewed the nasal preparations available on the Pharmaceutical Schedule. The Subcommittee considered that having an alternative, fully funded nasal preparation would be useful.

4 Omalizumab

Application

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4.1 The Subcommittee reviewed an updated application from Novartis New Zealand limited (Novartis) for the listing of omalizumab on the Pharmaceutical Schedule for the treatment of allergic asthma.

Recommendation

4.2 The Subcommittee **recommended** that omalizumab be listed on the Pharmaceutical Schedule with a medium priority. The Subcommittee recommended that PHARMAC develop Special Authority criteria for treatment of the small group of patients with severe allergic asthma that is not well controlled by other pharmaceuticals.

4.3 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; and (iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

4.4 The Subcommittee reviewed previous PTAC and Respiratory Subcommittee meeting minutes and noted that an application to list omalizumab for the treatment of severe allergic asthma had been reviewed by PTAC at its' May 2007 meeting and referred by the Committee to the Respiratory Subcommittee for its opinion.

The Subcommittee reviewed the application at its meeting held in June 2007 and recommended declining the application.

4.5 The Subcommittee noted that omalizumab is indicated for the reduction of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent, and children 6 years and older, with severe persistent allergic asthma who have IgE levels ≥ 30 IU/mL, a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with optimised asthma therapy.

4.6 The Subcommittee noted that there had been a number of applications for the funding of omalizumab through the Named Patient Pharmaceutical Assessment Pathway (NPPA) and these had led to a recommendation from the NPPA Panel that omalizumab be reassessed by PTAC or its Respiratory Subcommittee.

4.7 The Subcommittee noted the evidence from the following studies:

- The Exalt Study. Bousquet et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy 2011 May;66(5):671-8.
- Lanier B, Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol. 2009 Dec;124(6):1210-16.
- Hanania NA, et al Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. 2011; 154(9):573-82.
- Busse et al .Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;364(11):1005-15.
- Ohta et al. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. Respirology 2009;14(8):1156-65.
- Costello RW et al. Therapy with omalizumab for patients with severe allergic asthma improves asthma control and reduces overall healthcare cost. Ir J Med Sci. 2011 Sep;180(3):637-41
- Holgate et al. Efficacy and safety of a recombinant ant-immunoglobulin E antibody (omalizumab) in severe allergic asthma. J Clin Exp Allergy. 2004 Apr;34(4):632-8.
- Humbert M. et al Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005 Mar;60(3):309-16.
- Walker et al Anti-IgE For chronic asthma in adults and children (Review): the Cochrane Collaboration 2008.

4.8 Members noted that the additional studies published since omalizumab was first reviewed in 2007 have provided further evidence of the relative safety of the product. The Subcommittee noted that while the evidence for omalizumab is

moderate, the evidence base is still weak for this product for those severe asthmatics who have escalated to treatment with oral steroids.

4.9 The Subcommittee noted the following NICE guidelines

> 1.1 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:
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> - who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
> - only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.
>
> 1.2 Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.
>
> 1.3 People currently receiving omalizumab whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

4.10 Members noted that omalizumab, if funded, would require strict entry and exit criteria and facility for a trial of treatment. Members considered omalizumab may be appropriate for a small group of patients with severe persistent IgE–mediated asthma and it is important to define this target population. Members noted that strict entry and exit criteria would be required if omalizumab was funded and that there may be a role for a National Panel to assess the applications.

4.11 The Subcommittee reviewed a NPPA application for funding of omalizumab for an individual. All personal information had been removed from the application and a member of the Subcommittee who is involved in the patient's care left the room during the discussion. The Subcommittee noted the severity of disease, previous treatments, IgE status and the frequency of hospital admissions. Given the severity of disease, the number and length of the hospital admissions, the high IgE levels and the supporting information, the Subcommittee **recommended** that this NPPA application should be approved under the NPPA Policy.

4.12 The Subcommittee **recommended** that omalizumab should be listed on the Pharmaceutical Schedule with a medium priority subject to strict entry and exit criteria being defined. The Subcommittee instructed PHARMAC to undertake a financial assessment in order to define the patient group that would most benefit from treatment with omalizumab.

5 Extra fine beclomethasone diproprionate (QVAR)

5.1 The Subcommittee noted that the Asthma Subcommittee of PTAC has previously assessed an application from the original suppliers of QVAR (3M) dated September 1998. Members noted that chlorofluorocarbon (CFC)-containing inhalers have been phased out and replaced with hydrofluoroalkane (HFA)-based alternatives. Members noted that the reformulation provided the opportunity to improve the

inhalation technology and physical characteristics of corticosteroid formulations. QVAR contains HFA-beclomethasone dipropionate (HFA-BDP) with the steroid in solution rather than suspension, which, in combination with improved inhaler technology, produces an extrafine aerosol with a mass median aerodynamic diameter of 1.1 microm (smaller than the 3.5-4.0 microm found with CFC-BDP).

5.2 The Subcommittee noted that it has been demonstrated that the smaller particle size of QVAR is deposited in the lung to a greater extent than the deposition found with CFC-BDP, particularly in the small airways, a major site of inflammation. Increased lung deposition of QVAR permits a reduction in dosage relative to CFC-BDP. Members noted that clinical evidence confirms that adult and elderly patients required approximately half the dose of QVAR to achieve the same degree of asthma control as with CFC-BDP. In long-term assessments, patients taking CFC-BDP could be switched to QVAR at half the daily dose without exacerbation of their asthma symptoms. QVAR was associated with a low overall incidence of side effects and, at the maximum recommended dose of 640 microg/d, caused no more adrenal suppression than 672 microg/d CFC-BDP.

5.3 The Subcommittee noted the following evidence:

- Aubier et al Resp Med (2001) 9, 212-220 (Annex One) An 8 week open study to demonstrate the equivalence of HFA-BDP (QVAR) 800 mcg per day and HFA-FP (Fluticasone) 1,000 mcg per day in moderate to severe asthma.101 patients were randomised to HFA-BDP and 97 randomised to HFA-FP. The primary efficacy outcome was the mean change from baseline in morning peak expiratory flow at week 8. The study demonstrated that HFA-BDP at a dose of 800 mcg per day provided at least the same efficacy and safety as HFA-FP at a dose of 1000 mcg per day.

- Cochrane Review 2010. Lasserson et al Fluticasone versus 'extrafine' HFA-beclomethasone dipropionate for chronic asthma in adults and children (Review) The authors included 9 studies in their review. The authors concluded that the available evidence indicates that there is currently no statistical difference between FP and extrafine HFA-BDP in terms of change in FEV_1 over a period of 6-12 weeks in adults with moderate to severe asthma. They commented that this should not be interpreted as equivalence, as they could not exclude meaningful benefit of FP over HFA-BDP. There was insufficient data for the authors to generalise the finding to children. The results and conclusion of the review was Indacaterol increased 24 hour post-dose FEV1 after 12 weeks by 170 ml versus placebo and 100 ml versus formoterol and that once daily indacaterol is an effective 24 hour bronchodilator with significant value for COPD patients, providing clinical benefits over twice-daily formoterol for one year without loss of effect and with a favourable safety profile.

- Colice et al J Allergy Clin Immunol (Article in Press 2013). A large retrospective matched cohort study examined databse markers of asthma control from a US healthcare claims database. The objective was to compare real-life asthma outcomes and costs of extrafine HFA beclomethasone and fluticasone administered through a pressurized metered-dose inhaler. The authors concluded that in this study, patients prescribed HFA-beclomethasone as an initial ICS had similar or better asthma outcomes at lower doses compared with those prescribed fluticasone. The distribution of

doses showed that all patients in the HFA-beclomethasone cohort were prescribed 320 mcg per day whereas 46% of patients in the fluticasone group were prescribed a dose of 880 mcg per day (median dose 440 mcg per day). There were similar rates of treatment success for the HFA-beclomethasone and fluticasone cohorts; however those in the HFA-beclomethasone cohort had lower respiratory-related hospitalisations and referrals; were less likely to use a SABA dose of greater than 180 mcg per day; or to change therapy than those in the fluticasone cohort.

- Molimard et al Resp Med (2005)99,770-778. An open label, phase IV, randomised study, on the intake of LABAs stratified (2:1). N = 460 patients received QVAR Autohaler 800 mcg per day (n=149), fluticasone diskus 1000mcg per day (n=149) or budesonide Turbuhaler 1600 mcg per day (n=162) during 12 weeks. There was no statistical difference between the adverse events experienced by the treatment groups. The mean change from baseline was similar in the three treatment groups with no significant treatment effect. For patients treated with LABAs the change from baseline was higher in the QVAR Autohaler group. The 95% confidence intervals showed the non-inferiority of QVAR Autohaler compared to fluticasone and also demonstrated a statistically significant superiority of QVAR Autohaler compared to budesonide.

- Nayak et al Chest; 2002;122:1956-1965. Twelve week multicentre, randomised, double-blind, placebo controlled, parallel- group study. N = 353 children aged 5 to 12 years with moderate symptomatic asthma. The primary outcome measure was the mean change from baseline in $FEV_{1.}$ Secondary outcome measures were morning and evening peak expiry flow, daily asthma symptom scores and total LABA use. Similar proportions of patients reported at least one adverse event in the treatment cohorts and there were no differences in the tolerability. Treatment with HFA-BDP (80 mcg per day and 160 mcg per day) produced a significant, dose related increase from baseline in FEV_1 percent predicted, compared with placebo. At week 12, the changes were 9.2% ($p \leq 0.01$ vs placebo) and 10% ($p \leq 0.01$ vs placebo), and 3.9% for the HFA-BDP 80 mcg per day, HFA-BDP 160 mcg per day, and placebo groups respectively.

- Ruff et al Pediatric Asthma, allergy & Immunology; 2003;16:1-13 A twelve week randomised study where 319 patients were assigned treatment with 100 mcg per day HFA-BDP (n=108); 200 mcg per day HFA-BDP (n=104) or HFA-placebo (n=107) in order to determine whether HFA-BDP is effective in controlling asthma in children at a total dose as low as 100 mcg per day. The primary efficacy measurement was mean change from baseline in FEV_1 percent predicted at the end of the study. In the intent-to-treat analysis, mean change from baseline in FEV_1 percent predicted was 7.7% in the HFA-BDP 100 mcg per day group, 3.0% in the HFA-BDP 200 mcg per day group and 2.5% in the HFA-placebo group. Most of the adverse events reported were related to asthma symptoms or other respiratory complaints; fewer patient in the 100 mcg per day group reported adverse events than in the 200 mcg and placebo groups.

5.4 Members noted that the reasons for not approving the listing application in 1998 had largely been addressed by the clinical trials that had been undertaken and published since that date. Members noted that, in children, the main absorption

pathway of beclomethasone is via the oral mucosa and questioned if, due to the higher deposition of extrafine beclomethasone dipropionate in the lungs, there is less beclomethasone available systemically.

5.5 The Subcommittee noted that extrafine beclomethasone can be considered to be equivalent to other corticosteroids used with spacers.

5.6 The Subcommittee **recommended** that extrafine beclomethasone diproprionate be listed with a **medium** priority.