



PHARMAC responds on long-acting inhalers for COPD

Dr David Jones has recently written in the Journal (<http://www.nzma.org.nz/journal/118-1222/1669>)¹ about access to long-acting inhaled bronchodilators for patients with chronic obstructive pulmonary disease (COPD). We make some observations:

Tiotropium is already available but is under-used

Tiotropium has been funded for patients with severe COPD ($FEV_1 < 40\%$ predicted) since February this year. Details of Special Authority criteria can be found in Appendix 1 at the end of this letter.

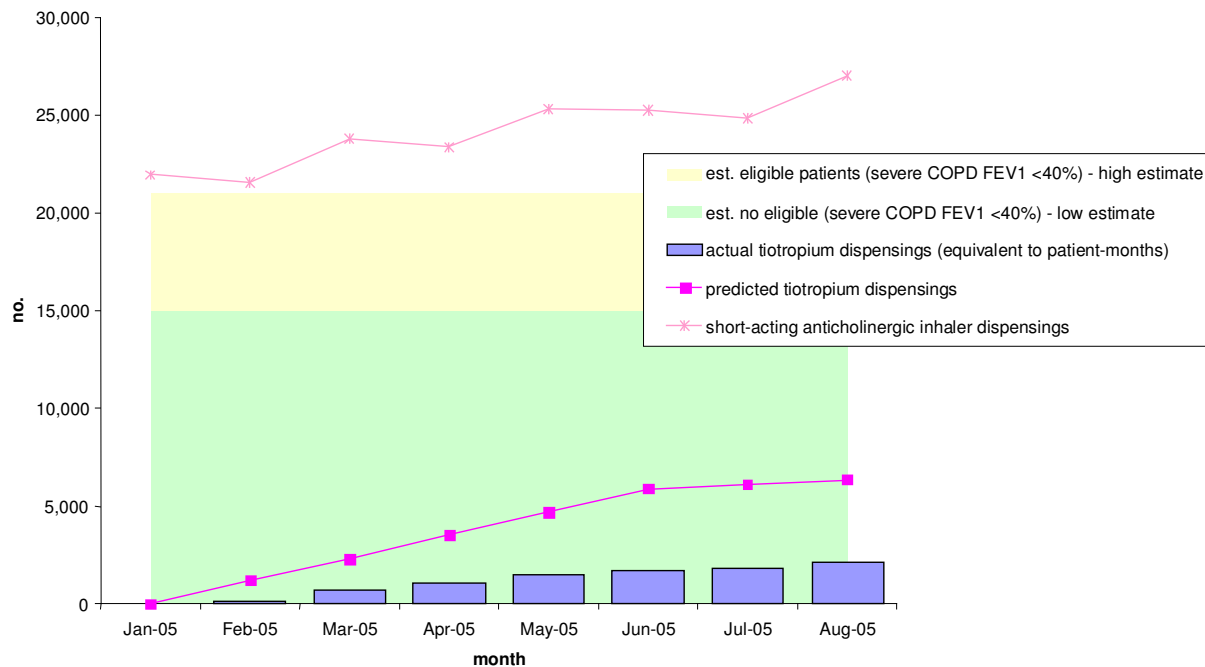
The Pharmacology and Therapeutics Advisory Committee (PTAC) in August 2004 considered tiotropium to be beneficial^{2,3} and cost-effective, and recommended that tiotropium be listed with a high priority (http://www.pharmac.govt.nz/latest_PTAC_minutes.asp).

For patients with severe COPD, tiotropium appears to be cost effective compared with other new medicines, with a cost per QALY of \$8,400.⁴ This includes major reductions in hospitalisations for COPD exacerbations (although there is an overall cost to the health sector from using tiotropium over ipratropium).

However, patients with severe COPD are not yet getting this effective treatment. The uptake of tiotropium since the February listing has been low:

- The prevalence of COPD—and numbers of patients eligible for tiotropium treatment—can be difficult to quantify,^{5,6} with wide-ranging estimates according to the definitions of COPD used.⁷ A possible range is between 65,000 and 85,000 patients with COPD,⁸ with perhaps one-quarter having severe COPD at the level of $FEV_1 < 40\%$ predicted.⁹ Hence there may be 15,000 to 21,000 patients with severe COPD ($FEV_1 < 40\%$ predicted).
- PHARMAC had estimated actual usage (numbers of patients using tiotropium) would be 5,900 by June 2005 (28–39% of the 15–21,000 eligible), reaching perhaps 11,200 patients by June 2007 (53–75%).
- However, HealthPAC data indicate there were 1,690 dispensings for tiotropium in June 2005, being 29% of what had been predicted.
- Currently (September 2005) there are perhaps 2,200 patients using tiotropium (2,146 dispensings), being 10–14% of eligible patients and 7% of users of both short-acting anticholinergics and long-acting beta agonists (LABAs)¹⁰—see Figure 1 below:

Figure 1. Uptake of tiotropium for COPD in New Zealand



The uptake of tiotropium in New Zealand has been one-quarter that of Australia over the comparable time period since listing¹¹—see Appendix 2 (at the end of this letter) for further details.

Extending access to tiotropium for less severe COPD

PTAC has previously considered, at its August 2004 meeting, the clinical benefits of a commercial proposal that included widening tiotropium access to FEV₁ < 60% predicted. This access was more than had been recommended by PTAC's Respiratory subcommittee,¹² possibly doubling the number of users.¹³ PTAC was unenthusiastic about this proposal, noting a lack of evidence at the FEV₁ 40–59% level and commenting on the likely extra patient numbers.

Further details can be found in the minutes of PTAC's meeting of August 2004, available online at http://www.pharmac.govt.nz/latest_PTAC_minutes.asp (item 'Tiotropium [Spiriva] for use in COPD' on page 8).

PTAC has now received a reapplication from the supplier to extend tiotropium access to FEV₁ < 60% predicted. This reapplication has been placed on the agenda for PTAC's next quarterly meeting.

Long-acting beta agonists (LABAs)

International guidelines/guidance (COPDX/TSANZ,¹⁴ GOLD,¹⁵ NICE¹⁶) to date do not differentiate between LABAs and long-acting anticholinergics in the treatment of COPD. However, as Dr Jones suggests, tiotropium may be better than LABAs for treating COPD,¹⁷ with some head-to-head trials showing significant FEV₁

improvements with tiotropium,^{18–20} others a trend to tiotropium but no significant differences,^{21–24} and possible tolerance to salmeterol.²⁵ Some trials show little improvement with LABAs compared with placebo in some measures.^{20,26} This area requires a more systematic analysis.

PTAC in the past has recommended against funding LABAs for COPD. PTAC considered an application for eformoterol (as Foradil) for COPD in August 2001, which it recommended be declined because of the absence of good evidence of meaningful effects. PTAC considered the evidence for Symbicort for COPD in May 2004, which PTAC considered to be weak and did not show any clear benefit, and recommended that this application be declined.

The Cochrane review of LABAs in COPD²⁷ was less than enthusiastic, concluding “In the few studies that could be included in this review, treatment of patients with COPD with long acting beta-2 agonists produces only small increases in FEV₁. The improvement in airways function does not seem to be associated with a consistent effect on other outcomes such as health related quality of life or reductions in breathlessness.”

Finally, we are aware of at least two RCTs comparing the LABA eformoterol with ipratropium (a short-acting anticholinergic).^{28,29} These trials show no significance between the two drugs—in contrast to the large effects seen between tiotropium and ipratropium.² One-third of publicly-funded LABA use in New Zealand is by patients aged 65 years and over.^{31–33}

Scott Metcalfe
Public Health Physician
Wellington

Sean Dougherty
Therapeutic Group Manager
PHARMAC
Wellington

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Sean Dougherty declares no conflicts.

Endnotes and references:

1. Jones D. Long-acting inhaled bronchodilators for COPD—lack of logic continues. *N Z Med J.* 2005;118(1222). URL: <http://www.nzma.org.nz/journal/118-1222/1669/>
2. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, Cornelissen PJ; Dutch/Belgian Tiotropium Study Group. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J.* 2002 Feb;19(2):209-16.
3. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, Menjoge SS, Serby CW, Witek T Jr. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J.* 2002 Feb;19(2):217-24.
4. Listing of tiotropium on the Pharmaceutical Schedule for COPD. PHARMAC Technology Assessment Report No. 59, November 2004.
5. COPD prevalence. *Bandolier* July 2003. <http://www.jr2.ox.ac.uk/bandolier/band113/b113-3.html>

6. Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? *Chest*. 2003 May;123(5):1684-92.
7. Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Respir J*. 2003 Aug;22(2):268-73.
8. Based on various extrapolations from empirical survey data and mathematical models from both New Zealand and elsewhere, numbers of patients with COPD in New Zealand appear to range anything from 40,000 to 200,000 depending on the source, but likely numbers might be 66,000 to 84,000 (M Tobias MoH personal communication; ABDS COPD data at http://www.aihw.gov.au/bod/bod_yld_by_disease/m_respiratory/m3_othresp.xls; Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1985 Jul;132(1):25-9.; Media release 'Huge Under Diagnosis of COPD in New Zealand' 15 March 2004 http://www.otago.ac.nz/news/news/2004/15b-03-04_press_release.html).
9. Patients with more severe disease with FEV1 <40% will comprise less than one quarter of patients with COPD – where in an Australian study, FEV1 <50% comprised 24% of all patients with COPD (FEV1 <70% predicted without dr-diagnosed asthma). (PHARMAC analysis of Busselton data 1994/95 from ABDS at http://www.aihw.gov.au/bod/bod_yld_by_disease/m_respiratory/m3_othresp.xls – original 1981 study from Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1985 Jul;132(1):25-9)
10. 30,691 dispensings of short-acting anticholinergic agents during September 2005, with 31,853 dispensings of LABAs including Symbicort.
11. PHARMAC analysis of: HealthPAC dispensing data; PBS data at http://www.medicareaustralia.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml, using PBS codes (<http://www1.health.gov.au/pbs/scripts/listtherlv11.cfm?sched=GA>) 1540C for tiotropium, 8135E, 8279R, 1541D, 1542E, 8238N, 1543F for ipratropium); population data at <http://www.stats.govt.nz/> and <http://www.abs.gov.au/Ausstats/>
12. The supplier had requested the Special Authority criteria be amended to remove the requirement for ipratropium and to increase the FEV1 threshold. The proposed criteria from Boehringer Ingelheim would remove the need for a patient to try ipratropium initially, and also would allow access to tiotropium to those patients with less (i.e. moderately) severe COPD (with FEV1s between 40% and 60% of predicted). This would be in addition to the patients included in the criteria recommended by the Respiratory Subcommittee of PTAC.
13. The likely impact of extending access criteria on patient numbers is difficult to quantify, because of a lack of good epidemiological data. However, suggests numbers of eligible patients could at least double (analysis of Australian survey data), but how this translates to uptake is not known.

PHARMAC staff have only been able to identify epidemiological data from Australia (Busselton), which was restricted to stratifying FEV1s only as low as < 50% of predicted. Analysis suggests that of those patients with COPD (FEV1 < 70% of predicted AND absence of doctor-diagnosed asthma) – who accounted for 6.2% of adults – one quarter had an FEV1 < 50% of predicted (1.5% of adults), and one half had had an FEV1 < 60% (2.8% of adults – RR <60%/<50% = 1.92). Although the Busselton data do not extend as low as FEV1s < 40%, the above data would suggest that, under Boehringer Ingelheim's proposed extended criteria, numbers of eligible patients could at least double.

PHARMAC analysis of Busselton data 1994/95 from ABDS at http://www.aihw.gov.au/bod/bod_yld_by_disease/m_respiratory/m3_othresp.xls - original 1981 study from Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1985 Jul;132(1):25-9.

14. McKenzie DK, Frith PA, Burdon JGW, Town GI. The COPDX Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2003.

Med J Australia 2003 178(6 Suppl 17 Mar): S1-S40.
http://www.mja.com.au/public/issues/178_06_170303/tho10508_all.html; Chronic Obstructive Pulmonary Disease (COPD). Australian and New Zealand Management Guidelines and the COPD Handbook, <http://www.nzgg.org.nz/guidelines/0073/COPDHandbook.pdf> (November 2002)

15. Global Initiative for Chronic Obstructive Lung disease. National Heart, Lung and Blood Institute and WHO. 2004 Update. <http://www.goldcopd.com/>
16. National Collaborating Centre for Chronic Conditions. Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care. Draft for second stakeholder consultation, November 2003 http://www.nice.org.uk/pdf/COPD_Fullguideline_2ndconsultation.pdf
17. PubMed search keywords tiotropium (salmeterol or eformoterol or formoterol) RCTs, date 30 September 2005
18. Briggs DD Jr, Covelli H, Lapidus R, Bhattacharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulm Pharmacol Ther.* 2005;18(6):397-404. Epub 2005 Apr 25.
19. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, Mueller A, Cornelissen PJ. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J.* 2005 Aug;26(2):214-22.
20. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, Kesten S, Towse L. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest.* 2002 Jul;122(1):47-55.
21. Cazzola M, Noschese P, Salzillo A, De Giglio C, D'Amato G, Matera MG. Bronchodilator response to formoterol after regular tiotropium or to tiotropium after regular formoterol in COPD patients. *Respir Med.* 2005 May;99(5):524-8. Epub 2004 Nov 26.
22. Balloira Villar A, Vilarino Pombo C. [Bronchodilator efficacy of combined salmeterol and tiotropium in patients with chronic obstructive pulmonary disease] *Arch Bronconeumol.* 2005 Mar;41(3):130-4.
23. Cazzola M, Centanni S, Santus P, Verga M, Mondoni M, di Marco F, Matera MG. The functional impact of adding salmeterol and tiotropium in patients with stable COPD. *Respir Med.* 2004 Dec;98(12):1214-21.
24. Cazzola M, Di Marco F, Santus P, Boveri B, Verga M, Matera MG, Centanni S. The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm Pharmacol Ther.* 2004;17(1):35-9.
25. Donohue JF, Menjoge S, Kesten S. Tolerance to bronchodilating effects of salmeterol in COPD. *Respir Med.* 2003 Sep;97(9):1014-20.
26. Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax.* 2003 May;58(5):399-404. Erratum in: *Thorax.* 2005 Feb;60(2):105.
27. Appleton S, Poole P, Smith B, Cates C, Veale A, Bara A. Long-acting beta2-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation (Cochrane Review). In: *The Cochrane Library, Issue 4, 2004.* Chichester, UK: John Wiley & Sons, Ltd.
28. Wadbo M, Lofdahl CG, Larsson K, Skoogh BE, Tornling G, Arwestrom E, Bengtsson T, Strom K; Swedish Society of Respiratory Medicine. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. *Eur Respir J.* 2002 Nov;20(5):1138-46.
29. Liesker JJ, Van De Velde V, Meysman M, Vincken W, Wollmer P, Hansson L, Kerstjens HA, Quint U, Pauwels RA. Effects of formoterol (Oxis Turbuhaler) and ipratropium on exercise capacity in patients with COPD. *Respir Med.* 2002 Aug;96(8):559-66.

30. PHARMAC analysis of one-way encrypted NHI-annotated dispensing claims data from the PharmHouse data warehouse for inhaled corticosteroids (ICSs), inhaled long-acting beta-agonists (LABAs) and inhaled/oral short-acting beta-agonist relievers (SABAs), for the period July 1999 to June 2004. 36% of dispensings for LABAs (including Symbicort) during 2003/04 were for patients aged 65 years and over – being 55,339 LABA dispensings in patients aged 65+ during 2003/04 out of 167,695 total LABA dispensings 2003/04.
31. The endorsement criteria for eformoterol 6mcg (Oxis 6) and the Special Authority criteria for Oxis 12, salmeterol and eformoterol/budesonide (Symbicort) specify the use of LABAs for the treatment of asthma alone.
32. Selected morbidity data for publicly funded hospitals 2000/01. Wellington: New Zealand Health Information Service, Ministry of Health, 2004. Table 1, ICD10 codes J45-6 (asthma), codes J40-44 (COPD). 5% of admissions during 2000/01 for asthma were for patients aged 65+ (392/8557), whereas 71% of COPD admissions were aged 65+ (6198/8675), and any admission for obstructive respiratory disease in a patient aged 65+ is 16 times more likely to for COPD than asthma (6198/392).

Appendix 1. Special Authority criteria for tiotropium (from 1 February 2005)

Special Authority for Subsidy

Initial application only from a general practitioner or relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

- 1 To be used for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD; and
- 2 In addition to standard treatment, the patient has trialled a dose of at least 40 mcg ipratropium q.i.d for one month; and
- 3 The patient's breathlessness \geq grade 4 according to the Medical Research Council dyspnoea scale (see note). Grade must be stated on the application; and
- 4 $FEV_1 < 40\%$ of predicted (copy of actual result and predicted value to be included in application, or values to be stated on form); and
- 5 Either:
 - 5.1 Patient is not a smoker; or
 - 5.2 Patient is a smoker and been offered smoking cessation counselling; and
- 6 The patient has been offered annual influenza immunisation.

Renewal only from a general practitioner or relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

- 7 Patient is compliant with the medication; and
- 8 Patient has experienced improved COPD symptom control (prescriber determined); and
- 9 Applicant must supply recent measurement of FEV_1 (% of predicted). Details must be attached to the application (for reporting purposes only).

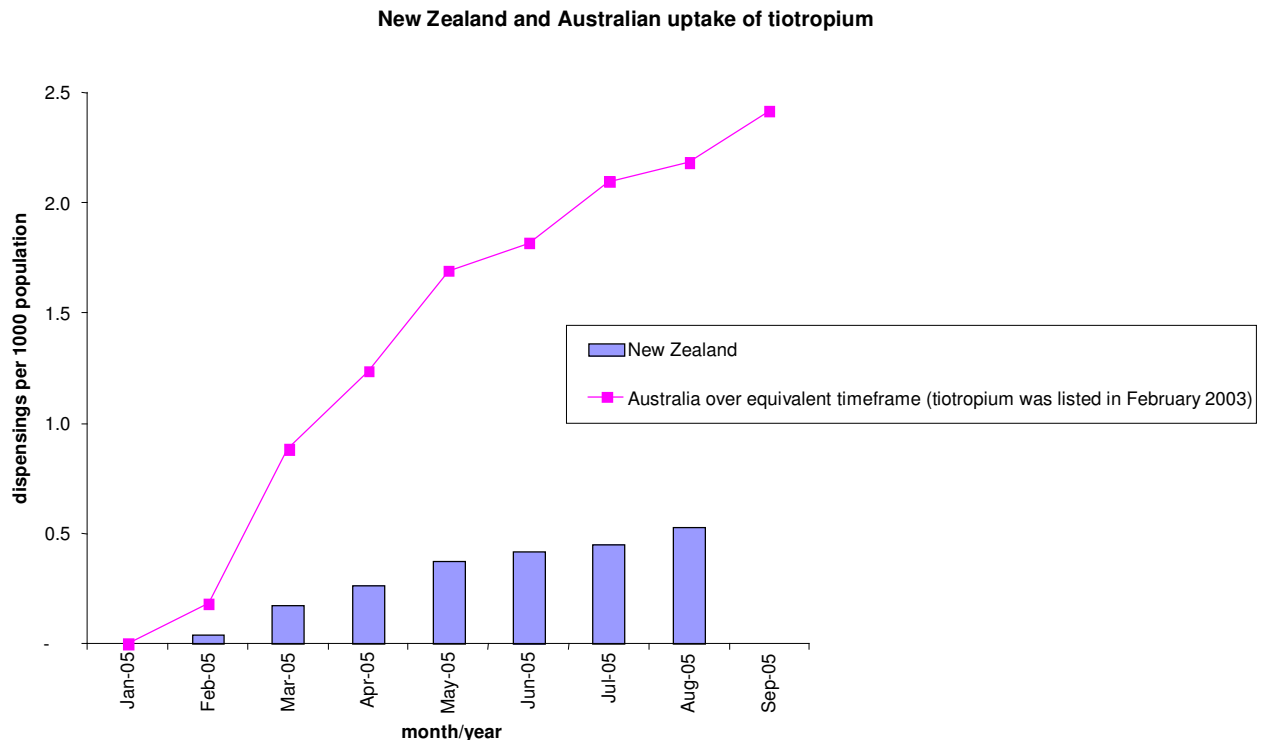
Note

Grade 4 (Medical Research Council dyspnoea scale) = stops for breath after walking about 100 metres or after a few minutes on the level; Grade 5 = too breathless to leave the house, or breathless when dressing or undressing.

Appendix 2. Uptake of tiotropium in Australia

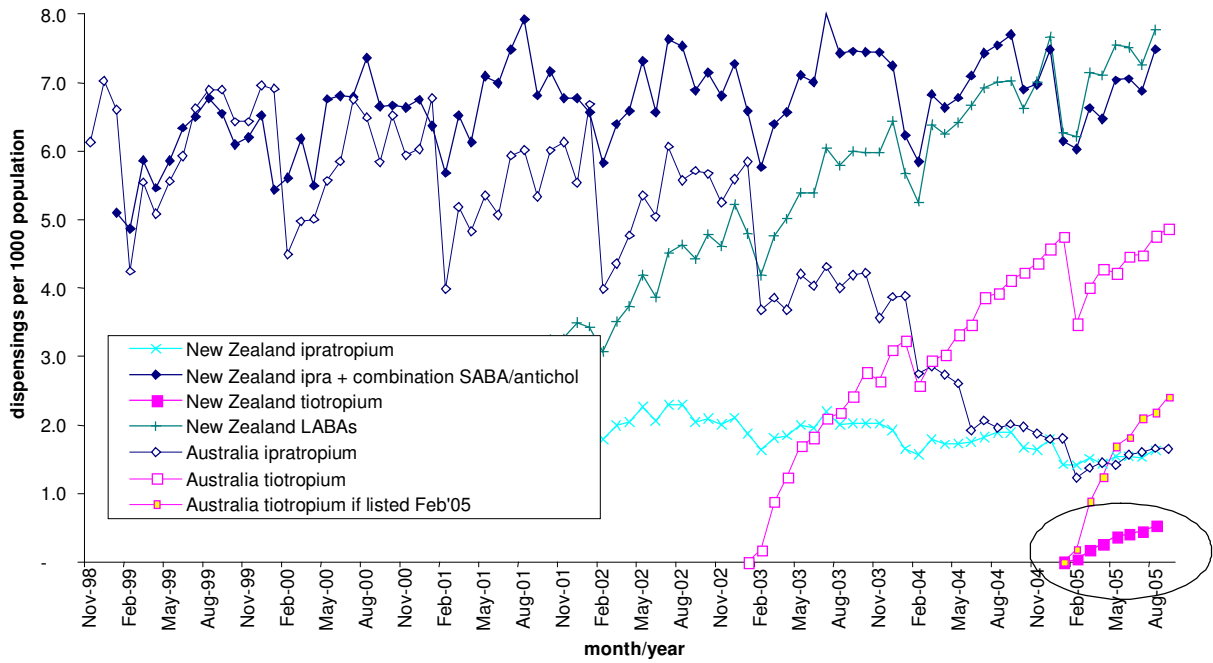
Tiotropium has been funded in Australia since February 2003 under a restricted benefit for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD.

The uptake of tiotropium in New Zealand has been one quarter that of Australia over the comparable time period since listing.¹¹ New Zealand had 2,146 dispensings (5.2 per 10,000 population) during September 2005. This compares with 43,451 dispensings (22.8 per 10,000) in Australia during August 2003, the seventh month that tiotropium was listed there – as can be seen in the following graphs.



Source: PHARMAC analysis of HealthPAC dispensing data (New Zealand), Pharmaceutical Benefits Scheme (PBS) services data (Australia), and population data for both countries.¹¹

New Zealand and Australian uptake of anticholinergic inhalers



Source: PHARMAC analysis of HealthPAC dispensing data (New Zealand), Pharmaceutical Benefits Scheme (PBS) services data (Australia), and population data for both countries.¹¹