Pharmaceutical Benefits Scheme

Post-market Review of

Chronic Obstructive Pulmonary Disease Medicines

ToR 6

Final Report

August 2017

Contents

List of Tables

Section 6: ToR 6
Need for a review of cost-effectiveness

Evaluate if the current utilisation of multiple therapies and the latest evidence relating to safety and efficacy justifies a review of cost-effectiveness for some or all medicines indicated for COPD.

1.1 Key findings for ToR 6

The key findings from this Review regarding the cost-effectiveness of COPD medicines are:

Utilisation

- From a cost and QUM perspective, the key concern identified by the Review is the growing proportion of patients initiating dual or triple inhaled therapy of the COPD medicines in scope (a quarter of patients). This is not recommended in the COPD-X Guidelines, is not in line with the PBS restrictions, and the cost-effectiveness of this use is unknown.
- NPS MedicineInsight data indicates that around 3.9% of patients recorded with a diagnosis of COPD only, and 6.1% of patients recorded with a diagnosis of COPD plus asthma, may have duplicated therapy.

Efficacy and safety

- Previous PBAC decision making has considered medicines in the LAMA, LABA, ICS/LABA and LAMA/LABA classes to be of comparable efficacy and similar safety to other medicines within their class. Where available, new evidence generally supports these decisions and the previously determined price relativities.
- PBS-listed LAMAs, LABAs and ICS/LABAs were all considered by the PBAC to be of comparative efficacy and similar safety and were cost-minimised. Overall, new evidence regarding the comparative efficacy and safety of LAMAs and LABAs compared to ICS/LABA FDCs is inconclusive, but does not support a change to previous PBAC decision making. No new evidence was identified that would change the previously determined price relativities for these therapies.

[redacted]

[redacted]

- There is evidence to support a modest benefit of stepping up from LAMA monotherapy to LAMA/LABA dual therapy. Based on four studies identified in this review, the mean difference in trough FEV_1 between LAMA alone and LABA/LAMA ranged from 28 mL (Singh et al, 2015b) to 112 mL (Maleki-Yazdi et al, 2014). It is worth noting that the PBAC has previously considered the MCID for change in trough FEV_1 was in the range of 100 to 140 mL. No studies were identified that examined the benefits of stepping up from LABA monotherapy to LAMA/LABA dual therapy.
- Of the four RCTs identified that compared LAMA monotherapy to LAMA/LABA dual therapy, the following PROs were reported: SGRQ (3 studies), rescue medication (2 studies), time to first exacerbation (1 study), and physiological response to exercise during SMETT (1 study). The SGRQ results from the TONADO 1 and 2 studies have previously been considered by the PBAC (Ferguson et al, 2015). Singh (2015b and 2016) concluded of the OTEMTO study that treatment with tiotropium/olodaterol versus tiotropium led to improvements in lung function over tiotropium that "were translated into clinically significant improvements in symptoms and health-related quality of life". Maleki-Yazdi (2014) showed that time to first exacerbation favoured dual therapy over monotherapy with marginal statistical significance.
- Several RCTs were identified that examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs. In general, these studies found LAMA/LABA FDCs provide superior efficacy and similar safety to ICS/LABA FDCs in COPD patients.
- No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS plus LAMA/LABA versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing these treatments in stable COPD (Tan et al, 2016). Thus it is uncertain if triple therapy is cost-effective over dual therapy with LABA/LAMA.

Stakeholder views (Forum and public consultations)

- PBAC recommendations are required to be considered in the context of the available clinical evidence and best practice guidelines. A number of stakeholders provided additional recent published evidence, including updates to guidelines and further utilisation analyses (refer to ToR 1 to 5, and Appendix U).
- A number of stakeholders were not supportive of a cost-effectiveness review of FDC inhalers for COPD, citing that:
    - The PBAC has previously established and accepted the cost-effectiveness of these medicines through a robust evaluation process.
    - The Review findings were insufficient to warrant a cost-effectiveness review.
    - The price disparity in combination products resulting from individual component drugs not being listed on the PBS has been remedied by the 2017 Strategic Agreement between Medicines Australia and the Department of Health.
    - Inappropriate prescribing may be managed by education and QUM measures.

- Utilisation data presented in the COPD review has limitations (refer to ToR 5) and over-estimates use outside guidelines and PBS restrictions.
- Concerns were raised regarding the Review conclusions relating to price relativities across classes of COPD medicines. COPD classes have different pharmacological properties, safety profiles and clinical places in therapy.
- Substantial reductions to the cost of PBS-listed COPD medicines will result from statutory price reductions in the 2017 Medicines Australia Strategic Agreement.
- Review outcomes should be implemented collaboratively over agreed timeframes.
- For further information, the Stakeholder Forum Summary is available at Appendix F.

1.2 Comparative efficacy and safety

The following section provides a summary of findings from ToR 3 and 4 of relevance to the cost-effectiveness of COPD medicines.

1.2.1 Monotherapy versus monotherapy in patients with COPD

Comparison of LAMAs

The review of new evidence found no significant differences in efficacy between the PBS-listed LAMA monotherapies, which is consistent with previous PBAC recommendations. Furthermore, there were no noteworthy safety findings and all LAMA monotherapies were well tolerated.

Comparison of LABAs

The previously established comparable clinical efficacy of indacaterol 150 µg and indacaterol 300 µg (both once daily) is supported by newer evidence from the INDORSE study (Chapman et al, 2011; good quality). Indacaterol demonstrated good overall tolerability and long-term safety in patients with moderate to severe COPD.

1.2.2 Monotherapy versus dual therapy in patients with COPDs

There is evidence of modest benefit of moving from LAMA monotherapy to LAMA/LABA dual therapy. However, it should be noted that many of the studies were only powered to detect a difference between LAMA/LABA dual therapy and placebo. This finding is consistent with previous PBAC decision making, where LAMA/LABA dual therapy was considered superior to LAMA monotherapy (July 2014). No studies were identified that examined the benefits of stepping up from LABA monotherapy to LAMA/LABA dual therapy.

The major submission for umeclidinium/vilanterol, considered at the March 2014 PBAC meeting, included a meta-analysis of two pivotal studies (DB2113360 and DB2113374) that compared umeclindium/vilanterol and tiotropium. [redacted]

To determine the relative pricing of the two products, [redacted]

The umeclidium/vilanterol (July 2014) minor PBAC submission presented a new trial which claimed an incremental benefit in FEV_1 of 112mL over tiotropium monotherapy. The Maleki-Yazdi (2014) trial was not evaluated.

In this review, five RCTs were identified that compared LAMA monotherapy to LAMA/LABA dual therapy. However, one study did not undertake statistical comparisons between monotherapy and dual therapy as the studies were not powered for this (Maltais et al, 2014). The tables from chapter 3 showing the mean change in trough FEV_1 for the remaining four studies are reproduced below (Tables 6.1 to 6.4).

Only the OTEMO 1 study did not show a statistically significant benefit in mean change in trough FEV_1 for LABA/LAMA dual therapy compared to LAMA alone (Singh et al, 2015b). The mean difference in trough FEV_1 between LAMA alone and LABA/LAMA ranged from 28 mL in the OTEMTO 1 study (Singh et al, 2015b) to 112 mL (Maleki-Yazdi et al, 2014). Two of the four studies did not produce benefits in trough FEV_1 that would generally be considered clinically meaningful by the PBAC, given their previous statement that the MCID for FEV_1 was in the range of 100 to 140 mL. [redacted]

Table 6.1 Least squares mean difference in trough FEV_1 – GLY/IND vs TIO

	Treatment difference GLY/IND vs TIO	p-value
LS mean difference in trough FEV_1 at 3 weeks, L	0.10 (0.05, 0.15)	<0.001

Source: Beeh (2014), Table 2.

Note: Treatment effects for each of the three cross-over periods were not reported separately.

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GLY, glycopyrronium; IND, indacaterol; LS, least squares; TIO, tiotropium.

Table 6.2 Adjusted mean trough FEV_1 after 24 weeks of treatment according to treatment history and GOLD classification – TIO/OLO vs TIO

	Adjusted mean (SE) FEV_1, mL				Treatment difference, mL, (SE)	95% CI	p-value
Treatment-naïve	**n**	**TIO/OLO**	**n**	**TIO**			
GOLD 2	226	146 (14)	237	68 (14)	79 (20)	40, 118	<0.0001
GOLD 3-4	193	148 (14)	206	79 (13)	69 (19)	32, 106	0.0002
Treatment-experienced	**n**	**TIO/OLO**	**n**	**TIO**			
GOLD 2	270	156 (13)	275	95 (13)	61 (18)	26, 97	0.0007
GOLD 3-4	328	118 (9)	299	76 (10)	41 (14)	15, 68	0.0023

Source: Ferguson (2015), Tables 3 and 4; Table S1 and S2 in online supplementary materials.

Note: Adjusted mean (SE) obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; OLO, olodaterol; SE, standard error; TIO, tiotropium.

Table 6.3 Trough FEV_1 in OTEMTO 1 and 2 after 12 weeks – ITT on full analysis set[a]

Difference in trough FEV_1, L	TIO/OLO vs TIO	TIO/OLO vs PBO	TIO vs PBO
	Mean (SE) [95% CI]	Mean (SE) [95% CI]	Mean (SE) [95% CI]
OTEMTO 1	0.028 (0.019) [–0.009, 0.066]	0.162 (0.019) [0.124, 0.200][b]	0.134 (0.019) [0.096, 0.172][b]
OTEMTO 2	0.039 (0.019) [0.002, 0.076][c]	0.166 (0.019) [0.129, 0.203][b]	0.127 (0.019) [0.090, 0.165][b]

Source: Singh (2015b), pg 1314 and Supplementary Table S2.

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; OLO, olodaterol; SE, standard error; TIO, triotropium.

Note: OTEMTO 1: placebo n=198; TIO n=200; TIO/OLO n=200. OTEMTO 2: placebo n=193; TIO n=197; TIO/OLO n=199.

a All patients who received at least one dose of study medication and had baseline and at least one post-baseline measurement for any of the primary endpoints.

b p<0.0001.

c p=0.0395.

Table 6.4 Treatment differences in least squares mean change from baseline – Trough FEV_1

LS mean change from baseline	UME/VIL 62.5/25		TIO 18		Treatment difference, L, (95% CI)	p-value
	n	Mean (SE)	n	Mean (SE)		
Trough FEV_1 at Day 84, L[a]	453	0.189 (0.0111)	449	0.081 (0.0113)	0.109 (0.078, 0.140)	<0.001
Trough FEV_1 at Day 169, L[b]	454	0.205 (0.0114)	451	0.093 (0.0115)	0.112 (0.081, 0.144)	<0.001

Source: Maleki-Yazdi (2014), Table 2 and Supplementary file 7.

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 and 5 min pre-dose on Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ITT, intention-to-treat; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

a Based on patients with analysable data for one or more visits.

b Primary outcome; ITT population.

Of the four RCTs identified that compared LAMA monotherapy to LAMA/LABA dual therapy, the following PROs were reported: SGRQ (3 studies), rescue medication (2 studies), time to first exacerbation (1 study), and physiological response to exercise during SMETT (1 study). The SGRQ results from the TONADO 1 and 2 studies (Ferguson et al, 2015) have previously been considered by the PBAC. Singh et al (2015b and 2016) concluded of the OTEMTO studies that treatment with tiotropium/olodaterol led to improvements in lung function over and tiotropium that "were translated into clinically significant improvements in symptoms and health-related quality of life". Maleki-Yazdi et al (2014) showed that time to first exacerbation favoured dual therapy over monotherapy with marginal statistical significance.

Comparison of LAMA or LABA monotherapy and ICS/LABA FDCs

Overall, new evidence regarding the comparative efficacy and safety of LAMAs and LABAs compared to ICS/LABA FDCs is inconclusive, but does not support a change to previous PBAC decision making, which considered these therapies generally comparable. ICS/LABA FDC was considered non-inferior to LAMA monotherapy in March 2007.

Three RCTs were identified that compared the efficacy and safety of LAMAs to ICS/LABA FDCs. Wedzicha (2008) found a similar rate of exacerbations between patients treated with fluticasone propionate/salmeterol compared to tiotropium, but significant improved risks in all cause mortality with the ICS/LABA treatment. Sarac (2016) found no significant difference in exacerbation risk between fluticasone propionate/salmeterol and tiotropium treatments, but the study may not have been sufficiently powered. Covelli (2016) compared the safety and efficacy of fluticasone furoate/vilanterol to tiotropium and found a similar improvement in

FEV_1, and comparable safety, although a minor increase in the number of pneumonia events in the fluticasone furoate/vilanterol group was observed.

No studies were identified that compared ICS/LABA FDC with a PBS-listed LABA monotherapy (i.e. indacaterol). However, one withdrawal trial was identified that found that patients with moderate airflow limitation and a history of no exacerbations in the previous year can safely withdraw from fluticasone propionate/salmeterol treatment to LABA (indacaterol) alone without any loss in efficacy in terms of FEV_1 and exacerbations (Rossi et al, 2014).

1.2.3 Dual therapy versus dual therapy in patients with COPD

Comparison of LAMA/LABA FDCs

Only two RCTs were identified that compared two LAMA/LABA dual therapy combinations (umeclidium/vilanterol FDC versus tiotropium plus indacaterol; and indacaterol/glycopyrronium versus tiotropium plus eformoterol). Compared with tiotropium plus eformoterol, patients receiving indacaterol/glycopyrronium showed a significantly increased pre-dose FEV_1 and FVC at week 26. Observed differences in lung function require further investigation because the trial was not designed to detect a minimally important difference in FEV_1 or FVC. Despite the limited body of evidence, the findings of these studies were consistent with previous PBAC recommendations; that is, there appears to be no significant difference in efficacy or safety between PBS-listed LAMA/LABA FDC therapies.

Comparison of LAMA/LABA dual therapy with ICS/LABA dual therapy

Several RCTs were identified that examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs. In general, these studies found LAMA/LABA FDCs provide superior efficacy and similar safety to ICS/LABA FDCs in COPD patients.

The FLAME trial is of particular interest as included patients had a history of one or more exacerbations in the previous 12 months. The FLAME trial demonstrated non-inferiority of glycopyrronium/indacaterol to fluticasone propionate/salmeterol and, on a subsequent subgroup analysis, superiority of the LAMA/LABA FDC to the ICS/LABA FDC based on exacerbation and lung function outcomes. However, there was no statistically significant difference between the FDCs in patients who had experienced two or more exaccerbations in the previous year.

Comparison of ICS/LABA FDCs

No new RCTs were identified that compared ICS/LABA FDCs. The review of safety of ICS use under ToR 4 found that there is some evidence for an intra-class difference for pneumonia risk between fluticasone and budesonide, favouring budesonide, but it is not conclusive. An ICS dose-response for pneumonia is apparent, but not conclusive.

1.2.4 Comparison of dual and triple therapy

Studies that investigated the benefit of adding a LAMA to ICS/LABA dual therapy showed that the step up from dual to triple therapy results in statistically significant and clinically meaningful improvements in trough FEV_1. The PBAC has previously seen evidence from the GLISTEN trial that demonstrated that glycopyrronium plus fluticasone propionate/salmeterol is statistically superior to fluticasone propionate/salmeterol alone in terms of trough FEV_1 (November 2015 PSD for glycopyrronium).

No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS plus LAMA/LABA versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing the treatment of stable COPD with ICS plus combination LAMA/LABA inhalers against combination LAMA/LABA inhalers alone (Tan et al, 2016).

1.3 Utilisation of COPD inhaled preventer medicines

The review of COPD medicines utilisation (ToR 5) identified a growing proportion of patients initiating dual and triple therapy for COPD in both the analysis of PBS data and MedicineInsight prescriber data. Initiation to combinations of the COPD medicines in scope is not supported by either the COPD-X guidelines or PBS restrictions, and has not been assessed as cost-effective by the PBAC.

The COPD-X guidelines and PBS restrictions support initiation of monotherapy preventers only for COPD. The analysis of PBS/RPBS claims data found that in 2016 around 26% of patients initiating a COPD medicine, initiated to combination therapy (up from around 15% in 2010). As patients initiating ICS/LABA were excluded from this analysis, this likely represents an underestimate. In 2016, around 15.6% initiated to LAMA plus LABA, 8.5% initiated triple therapy with ICS, LABA and LAMA, and 1.8% initiated duplicated therapies (i.e. therapies that involved the use of multiple medicines from the same class).

The analysis of NPS MedicineInsight data, found that 46.3% of COPD only patients initiated combinations of preventer medicines: 7.4% initiated LABA plus LAMA; 38.5% initiated ICS plus LABA; and a further 5.1% initiated triple therapy. MedicineInsight data also indicates that around 3.9% of COPD only and 6.1% of COPD plus asthma patients may have duplicated therapy, which presents an issue for both safety and cost-effectiveness.

At the Stakeholder Forum, stakeholders identified that many doctors prescribe ICS/LABA early in the treatment pathway of all respiratory conditions, partly because a diagnosis has not been initially confirmed and partly because ICS/LABAs were available on the PBS for some years before the listing of monotherapy LABAs and LABA/LAMA FDCs. The LFA Consumer Research Report found that some patients with COPD may be using antibiotics and oral steroids long-term, which may have QUM implications.