Response to Final Terms of Reference
COPD Post-market Review
22nd April 2016

Executive Summary

GlaxoSmithKline (GSK) recognises the Government's responsibility to maintain a robust and sustainable Pharmaceutical Benefits Scheme (PBS), and we further recognise that Post Market Reviews (PMRs) can play a role in ensuring the efficient use of medicines through Quality Use of Medicines (QUM) accessed via the PBS.

As one of Australia's leading suppliers of Chronic Obstructive Pulmonary Disease (COPD) medicines, GSK would like to take the opportunity to engage proactively and in good faith in this review and is committed to working with the review committee to provide relevant evidence based input.

GSK acknowledges the Government for its commitment to the agreed PMR framework and for an inclusive approach to consultation on a genuine QUM issue. The PMR framework was put in place to ensure transparency and integrity in the review process through clear visible steps, a consistency of approach, and to build trust between industry and Government by allowing forward planning for all stakeholders and avoiding ad hoc and unjustified outcomes from the process. Throughout this process, GSK welcomes the opportunity to provide feedback on the PMR framework as it relates on the suitability of data and the mechanisms for improving QUM available to Government.

GSK's response will explore potential ways for the broader COPD community to address key QUM issues. GSK has much experience in leading independent and partnered training programmes, including CPD accreditations, which are further detailed in the response to Term of Reference (TOR) 6. There are a number of initiatives and organisations that government can utilise to support the use of COPD medicines, including National Prescribing Service (NPS) educational initiatives for prescribers, QUM provisions in the 6th Community Pharmacy Agreement (6CPA) and recently announced chronic disease management reforms. These represent an ideal opportunity for COPD to be profiled and elevated as a significant chronic condition affecting Australians requiring attention.

The following table provides a summary of GSKs responses to the Terms of Reference:

Terms of Reference	Summary of GSK Position
1. Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines	• The relevant clinical guidelines in Australia are COPD-X and the GOLD strategy document • Current clinical treatment guidelines recommend an individualised approach to pharmacological treatment, based on the assessment of symptoms and exacerbation risk • PBS restrictions are broadly consistent with the treatment guidelines • Review required of the LABA/LAMA fixed dose combination product PBS restrictions to ensure alignment with treatment guidelines and intended place in therapy
2. Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines	• Important and clinically relevant outcomes for COPD patients include lung function, exacerbations and patient reported outcomes such as health status and health related quality of life • The clinical outcomes previously evaluated by the PBAC when affirming cost-effectiveness of GSK sponsored COPD treatments, remain valid and clinically relevant.
3. Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/LAMA, ICS/LABA and LAMA+ICS/LABA (separate items or FDCs) for the	• The COPD-X guidelines are updated regularly to incorporate relevant published medical literature and health care professionals receive update alerts • There are a number of publications available containing information relating to GSK products that the PBAC has not yet reviewed • The publications supplement the significant body of evidence existing regarding the safe and effective use of products within the GSK COPD portfolio

treatment of COPD and PBAC has not previously considered	• GSK recognises the evolving COPD treatment paradigm and is committed to ongoing clinical research in areas of unmet clinical need • There is emerging evidence exploring the use of triple combination therapy in COPD
4. Review the published literature on the safety of prolonged ICS use in monotherapy and in combination with LABA and/or LAMA for COPD that PBAC has not previously considered.	• There is a large body of evidence supporting the use of ICS in combination with LABA for COPD • The European Medicines Agency (EMA) reviewed the risk of pneumonia with ICS containing medicines in COPD and concluded that the risk/benefit remains positive • A number of recent publications, including a comprehensive Cochrane review, demonstrate that there is an increased risk of pneumonia associated with prolonged use of inhaled corticosteroid (ICS) in COPD patients, however there is no parallel increase in mortality. • The current evidence does not suggest any major differences in pneumonia between available combinations. • Recent evidence from clinical studies, not previously considered by the PBAC, confirm that ICS containing COPD regimens remain a safe and effective treatment option
5. Analyse the current utilisation of PBS listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions	• There are significant data limitations in the Medicare Australia data, which make assessment of the utilisation of COPD medications highly uncertain • Whilst there is extensive co-prescribing of COPD treatments, this use is largely consistent with treatment guidelines and PBS restrictions • GSK supports initiatives aimed at reducing inappropriate use of medicines of the same class • GSK is seeking consideration of a revision to the PBS restriction for *Anoro*, a LABA/LAMA fixed dose combination product, in order to align with treatment guidelines and its TGA listing and clarify its intended place in therapy
6. 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.	• The burden of COPD on the Australian public remains significant, despite improvements in treatment • The cost effectiveness of GSK medicines for COPD has already been established by a robust and rigorous PBAC process • Clinical outcomes previously presented to the PBAC for GSK medicines remain relevant and valid, and clinical data made available since the approval of these medicines is consistent with previously considered data • A review of the cost effectiveness of these medicines is not justified • QUM improvements in the treatment of COPD will benefit Australian patients and therefore should be the focus of the PMR • The government should leverage existing professional bodies and organisations, including the NPS, doctors and pharmacists (through 6-CPA), to drive improvements in QUM • GSK provides a summary of QUM considerations to realise the full benefit of COPD medicines for patients, government and taxpayers.

Scope

Ratified Terms of Reference

Accepting the available information, GSK has provided a summary of feedback for consideration.

1. ***Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines.***

Clinical Guidelines

The pivotal COPD reference points for Australian clinicians are the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2016) strategy document and the Australian and New Zealand COPD-X Plan (Lung Foundation Australia, 2015), collectively referred to as the 'guidelines' for the purposes of this PMR. Furthermore, the Respiratory Therapeutic Guidelines (Version 5, 2015) reference the COPD-X Guidelines for the appropriate management of COPD.

Table 1 - Summary of guidelines recommendations for COPD patients

Guidelines	Pharmacological Management of COPD
GOLD 2016*	Group A (low risk, less symptoms) [a] Recommended first choice: Short-acting muscarinic antagonist (SAMA) prn or short-acting beta$_2$-agonist (SABA) prn Alternative choice: Long-acting muscarinic antagonist (LAMA), or long-acting beta$_2$-agonist (LABA) or SABA + SAMA Other possible treatments: Theophylline Group B (low risk, more symptoms) [b] Recommended first choice: LAMA or LABA Alternative choice: LAMA + LABA Other possible treatments: SABA and/or SAMA, or theophylline Group C (high risk, less symptoms) [c] Recommended first choice: ICS + LABA or LAMA Alternative choice: LABA + LAMA, or LAMA + phosphodiesterase-4 inhibitor, or LABA + phosphodiesterase-4 inhibitor Other possible treatments: SABA and/or SAMA, or theophylline Group D (high risk, more symptoms) [d] Recommended first choice: ICS + LABA and/or LAMA Alternative choice: ICS+ LABA + LAMA, or ICS + LABA + phosphodiesterase-4 inhibitor, or LABA + LAMA, or LAMA + phosphodiesterase-4 inhibitor Other possible treatments: carbocysteine or N-acetylcysteine or SABA and/or SAMA, or theophyllines

Australian Lung Foundation Stepwise Management of Stable COPD 2015	For all symptomatic patients with COPD: • Follow a stepwise approach to pharmacological treatment until adequate control of breathlessness, functional capacity and exacerbation frequency is achieved. • Use short-acting inhaled bronchodilator therapy for short-term relief of breathlessness For patients receiving short-acting bronchodilators who have persistent troublesome dyspnoea, add a LABA or LAMA (or both in combination if monotherapy is not adequate) for regular use For patients with FEV1< 50% predicted and ≥2 exacerbations in 12 months: • Initiate an ICS + LABA fixed dose combination and discontinue LABA monotherapy • For patients with moderate-severe COPD with frequent exacerbations who are not receiving a LAMA, consider addition of a LAMA to the ICS+LABA For severe COPD (FEV1 < 40% predicted), consider adding low-dose theophylline (100mg twice daily) Avoid long-term (> 2 weeks) use of systemic corticosteroids

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference

Abbreviations: BUD, budesonide propionate; CAT; COPD assessment test, COPD, chronic obstructive pulmonary disorder; FOR, formeterol; FP, fluticasone propionate; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; MRC, Medical Research Council dyspnoea scale, SABA, short-acting β-agonist; SAL, salmeterol

[a] Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and no hospitalisation for exacerbation and CAT score < 10 or mMRC grade 0 -1

[b] Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and no hospitalisation for exacerbation and CAT score ≥ 10 or mMRC grade ≥ 2

[c] Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalisation for exacerbation and CAT score < 10 or mMRC grade 0 -1

[d] Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalisation for exacerbation and CAT score ≥ 10 or mMRC grade ≥ 2

Current clinical treatment guidelines recommend an individualised approach to pharmacological treatment, based on the assessment of symptoms and exacerbation risk. Inhaled bronchodilators constitute the primary pharmacological therapy for patients with COPD. Bronchodilators refer to medications that increase the FEV_1 or alter other spirometric variables, usually by altering airway smooth muscle tone (GOLD, 2016). Bronchodilators can be classified as either short- acting (effects lasting ≤6 hours) or long-acting (effects lasting ≥12 hours). Given this, short-acting bronchodilators are used primarily for the immediate relief of symptoms and exercise limitation, while long-acting bronchodilators are used as maintenance treatment for the reduction of persistent symptoms.

The use of long acting bronchodilator medications (such as LABAs and LAMAs), either alone or in combination is recommended in COPD patients characterised by persistent symptoms but with a low risk of exacerbations. In patients with an increased risk of exacerbations, it is recommended that an ICS component is used in combination with a long acting bronchodilator(s). This is based on evidence that regular treatment with an ICS in combination with a bronchodilator(s) reduces the frequency of exacerbations in symptomatic COPD patients. It is recommended that a short-acting bronchodilator is used on an 'as-needed' basis to relieve symptoms in combination with a long acting bronchodilator based treatment (McKenzie, Abramson, Crockett et al., 2010).

Consistent with treatment guidelines, the management of patients with COPD is currently differentiated based on exacerbation history, where patients who present with a history of exacerbations are typically initiated on an ICS/LABA and patients who are symptomatic in the absence of exacerbations are initiated on a LAMA or LABA (or both if monotherapy is not adequate) (McKenzie, Abramson, Crockett et al., 2010; GOLD, 2016).
As the disease progresses, the guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action (Celli,

2004; GOLD 2016). For patients with uncontrolled symptoms and/or repeated exacerbations, the incorporation of ICS or triple therapy, is recommended.

Guideline alignment with PBS restrictions

The COPD-X and GOLD Guidelines are broadly consistent with the current PBS restriction criteria for the ICS/LABA combination therapies *Seretide*® and *Breo*®, in that they limit therapy to patients with FEV_1 < 50% predicted and a history of repeated exacerbations.

The long-acting bronchodilator *Incruse*®, a LAMA, is listed for a non-specific population of patients with 'chronic obstructive pulmonary disease', consistent with its allocated place in therapy.

Flixotide®, an ICS, has appropriate clinical placement relative to currently available ICS treatments, available for a non-specific population of patients.

Serevent®, a LABA, whilst TGA indicated for use in COPD, is not listed on the PBS for this particular indication.

GSK believe the PBS restriction for *Anoro*®, a LABA/LAMA combination, is not entirely aligned with the guidelines or with its intended place in therapy. *Anoro* is an available option for patients who remain symptomatic in spite of treatment with a LAMA **or** LABA monotherapy who may need to 'step up' to combination treatment. In addition, there is also a defined clinical place for *Anoro* within the guidelines for patients presenting with persistent troublesome symptoms regardless of receiving short-acting bronchodilators.

Most patients receiving treatment with COPD maintenance medication will also require reliever therapy with a short-acting bronchodilator such as Ventolin® (salbutamol), a SABA, on an as-needed basis.

Conclusion

GSK believe that the prescribing restrictions for its PBS listed COPD medicines are largely consistent with treatment guidelines, with the exception of fixed dose combination (FDC) LABA/LAMA *Anoro*, a subject further explored in the response to TOR 5.

2. ***Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines.***

Clinical Importance of the outcomes

Clinical trials in COPD typically include FEV_1, the principal measure of lung function, as a primary outcome. This is reflected in previously accepted PBS submissions for COPD medicines.

The clinical importance of lung function measures can be attributed to the fact that the COPD research community and regulatory agencies have traditionally recognised FEV_1 as an objective and repeatable index of airflow obstruction that has the capacity to measure symptomatic relief and disease progression in patients with COPD (Cazolla et al., 2008). These assertions are based on a large body of data which demonstrate an increased risk of exacerbations, hospitalisation and death with worsening airflow limitation (Decramer et al., 2009; Hurst et al., 2010; Jenkins et al., 2009). In terms of health related quality of life (HRQoL), recent analyses have demonstrated a relationship between improved lung function as measured by trough FEV_1, and improvements in health status as measured by the St George's Respiratory Questionnaire (SGRQ) (Jones et al., 2011; Westwood et al., 2011), TDI (Transition Dyspnoea Index) and COPD exacerbation history in adult patients with stable COPD (Jones et al., 2011). The significance of FEV_1 in COPD is reflected by the fact that international bodies such as the GOLD, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) each promote the use of FEV_1 as a means of defining and staging COPD. Given this, COPD is commonly known as a 'disease state characterised by airflow limitation that is not fully reversible' (Celli et al., 2004).

Despite the importance of FEV_1 in characterising the COPD patient, it is not the only important treatment outcome. The complex nature of COPD means that it is important to assess treatment effectiveness in terms of a number of patient-reported outcomes. Clinical outcomes relevant to the assessment of exacerbations, dyspnoea, functional status, and health status are all recognised as being important for the characterisation of response to treatment (Cazzola et al., 2008). This is reflected in current treatment guidelines which specify that the goals of pharmacologic treatment in COPD are not only to maximise airflow, but to reduce symptoms, the frequency and severity of exacerbations, and improve health status and exercise tolerance (GOLD, 2015).

Regulatory guidelines also recognise that COPD can be a heterogeneous disease state and that measurement of lung function alone is insufficient. In Australia, the TGA has adopted (Effective: 15 September 2014) the European Medicines Agency scientific guideline for COPD 'Guideline on clinical investigation of medicinal products in the treatment of COPD' [EMA/CHMP/483572.2012 – corr1]. This guideline requires that in addition to the measurement of lung function (FEV1 being the parameter of preferred choice) that additional symptom-based or patient-based evidence is also required through the use of a co-primary endpoint.
The following list highlights appropriate efficacy endpoints described in the TGA-adopted EU regulatory guideline:

Lung function
*Changes in spirometric parameters should be measured as a relevant part of the overall effect of any new therapy in the treatment of patients with COPD.....**FEV1 is the most extensively used parameter for adopting treatment strategies in COPD**. FEV1 is one of the most repeatable lung function parameters and in COPD is a measure of the obstructive element of the disease.*

Exacerbations
The rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality and the usually significantly increased health-care requirement.
The frequency and/or severity of exacerbations are important outcome measures that should be considered in clinical studies in COPD. Such measures can include reduction in the number of exacerbations, annual rate and severity of exacerbations. Time to first exacerbation might also be considered.

Patients' and investigators' reported outcomes
Disease-specific questionnaires, dyspnoea and symptom scales are considered relevant outcomes for the characterisation of response to treatment.
Health status and HRQOL e.g. St George's Respiratory Questionnaire (SGRQ) and more recently the COPD Assessment Test (CAT)
Dyspnoea e.g. Transition Dyspnoea Index (TDI), MRC (Medical Research Council Dyspnoea Scale)

COPD symptom scales

Patients' questionnaires or diary cards

Exercise capacity

Rescue medication
The use of rescue medication (e.g. β2 agonist, reliever inhaler) reflects effects on symptoms and therefore can be considered as a clinical endpoint.

Composite scores

Imaging

Conclusion

Collectively, the measurement of FEV_1-based outcomes supplemented with other key patient-relevant outcomes related to dyspnoea (as assessed by the TDI or MRC), rescue-medication use, and HRQoL (as measured by SGRQ, CAT and EQ5D) remain valid and appropriate as per regulatory guidance and a substantial body of evidence. They are reflective of the accepted inclusion of COPD treatments on the PBS. As the PBAC must be convinced of the cost-effectiveness of a treatment prior to recommendation, the data reviewed to support these decisions was deemed acceptable and appropriate.

Future clinical trials for medicinal products may be aimed to modify the course of the disease and/or disease progression, however to date, no treatment has demonstrated an effect on disease progression apart from smoking cessation.

GSK sponsored Phase III clinical trial programmes (including future closed triple combination trials) have been designed taking into account validated and appropriate clinical endpoints for COPD trials.

3. ***Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/LAMA, ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for treatment of COPD that PBAC has not previously considered.***

GSK purports that there is already an existing established process in conducting regular and timely systematic review of published literature on the efficacy and safety of COPD medications. The COPD-X Guidelines, a joint project for the Thoracic Society of Australia and New Zealand (TSANZ) and the Lung Foundation Australia (LFA), integrates a rigorous examination of the relevant published medical literature on a quarterly basis to ensure the guidelines remain up to date. Health care professionals (HCPs) are advised of such updates via alerts through emails, newsletters, the LFA website and also via discussion at medical congresses.

A summary of new clinical evidence including recently published data regarding GSK sponsored products is provided in Table 2 below.

Table 2 – Recent clinical studies for GSK respiratory portfolio

GSK Product	Study Name/ID/Publication	Details of study
BREO	SUMMIT Vestbo J et al. Eur Respir J 2013; 41: 1017-1022 clinicaltrials.gov identifier NCT01313676 Press release (8th Sept 2015): https://www.gsk.com/en-gb/media/press-releases/2015/gsk-and-theravance-announce-results-from-the-summit-copd-cv-survival-study/	Study Design The 'Study to Understand Mortality and Morbidity in COPD' (SUMMIT) aims to determine the impact of FF/VI combination and the individual components on the survival of patients with moderate COPD and either a history of CVD or at increased risk of CVD. SUMMIT is a multicentre, randomised, double-blind, parallel-group, placebo-controlled trial of 16 000 patients with moderate COPD randomly assigned to once daily treatment with FF/VI (100/25µg), FF (100 µg), vilanterol (25 µg) or matched placebo. Mortality is the primary end-point; the study is an event-driven trial powered by the comparison of FF/VI versus placebo. Secondary endpoints are decline in FEV1 and effect on a composite cardiovascular endpoint. Patients are aged 40-80 years with a smoking history of ≥10 pack-years, a clinical diagnosis of COPD with $FEV_1/FVC<0.70$ and moderate airflow limitation (defined as post-salbutamol FEV_1 ≥50 and ≤70% of predicted normal values).As most patients with severe or very severe airflow limitation will require treatment with long-acting bronchodilators and possibly ICS, and because co-morbidities seem independent of severity of airflow limitation, the study will include patients with moderate airflow limitation only. In addition, patients are required to have a history of CVD or to be at increased risk for CVD. Results For the primary endpoint of the study, the risk of dying on FF/VI 100.25 µg was 12.2% lower than on placebo over the study period, which was not statistically significant (p=0.137). For the first of two secondary endpoints, FF/VI 100/25mcg reduced the rate of lung function decline (as measured by FEV_1) by 8mL per year compared with placebo (p=0.019). As the primary endpoint was not met, statistical significance cannot be inferred from this result. For the other secondary endpoint, the risk of experiencing an on-treatment cardiovascular (CV) event (CV death, myocardial infarction, stroke, unstable angina and transient ischemic attack [TIA]) at any time was 7.4% lower in patients taking FF/VI 100/25mcg versus placebo which was not statistically significant (p=0.475). The study also formally analysed a number of additional COPD endpoints

		assessing the efficacy of FF/VI relative to placebo, which included FEV_1 (post-bronchodilator), rate of moderate/severe exacerbations, time to first moderate/severe exacerbation, time to first severe (hospitalised) exacerbation, rate of severe (hospitalised) exacerbation, health related quality of life (as measured by the St George's Respiratory Questionnaire-COPD total score at 12 months) and health status as measured using the COPD Assessment Tool (CAT) at 12 months. Against these endpoints FF/VI demonstrated an improvement compared to placebo with a nominal P-value of $\leq$0.002 for each. As the primary endpoint was not met, statistical significance cannot be inferred from these results. The most frequently reported adverse events ($\geq$ 3% in FF/VI 100/25mcg and greater than placebo) were nasopharyngitis (FF/VI 100/25mcg 8.9%, placebo 7.5%), upper respiratory tract infection (FF/VI 100/25mcg 6.3%, placebo 4.8%), pneumonia (FF/VI 100/25mcg 5.0%, placebo 4.6%), back pain (FF/VI 100/25mcg 4.3%, placebo 3.5%), hypertension (FF/VI 100/25mcg 3.9%, placebo 3.3%) and influenza (FF/VI 100/25mcg 3.4%, placebo 2.9%). The incidence of on-treatment serious adverse events (SAEs) were 23.2% on FF/VI 100/25mcg and 22.2% on placebo. Adverse events of special interest included all related terms for CV adverse events and pneumonia. The incidence of CV adverse events was 17.8% on FF/VI 100/25mcg, 16.8% on placebo and serious CV adverse events was 8.5% on FF/VI100/25mcg, 7.7% on placebo. The incidence of pneumonia was 5.7% on FF/VI 100/25mcg and 5.2% on placebo and the incidence of serious pneumonia was 3.4% on FF/VI 100/25mcg and 3.1% on placebo. Conclusions Ambitious goal of demonstrating a reduction in death from any cause in patients with both COPD and CVD. Whilst the study was unable to demonstrate a statistically significant improvement on this endpoint, it provides clinicians with a wealth of data to understand the interplay between these two conditions and insights on how to improve the management of these patients. Breo 100/25µg continues to play an important role in the treatment of appropriate patients with COPD. Provides additional confidence in the safety and efficacy of Breo 100/25µg as a once-daily treatment to improve lung function and reduce exacerbation risk in patients with COPD.
INCRUSE	*Incruse* versus Tiotropium (Study 201316) clinicaltrials.gov identifier NCT02207829 Feldman G et al. International Journal of COPD 2016; 11: 719-730 *Incruse* versus Glycopyrronium (Study 201315) clinicaltrials.gov identifier NCT02236611	Two head-to-head studies directly comparing the efficacy and safety of *Incruse* (umeclidinium) to two available bronchodilator treatments, tiotropium (study 201316) or glycopyrronium (study 201315), when used by patients with COPD. Study Design Umeclidinium vs tiotropium (study 201316) This was a 12 week, multicentre, randomised, blinded study involving 1,259 patients, designed to compare the efficacy and safety of umeclidinium (62.5mcg once daily) administered via the Ellipta® inhaler to tiotropium (18mcg once daily) administered via the Handihaler inhaler in subjects with COPD. Patients were randomised 1:1 to umeclidinium 62.5mcg inhalation powder or tiotropium 18mcg. The primary endpoint was change from baseline in trough FEV_1 at Day 85. The primary analysis was to determine non-inferiority (based

	Press release: 20 Oct 2015 http://www.gsk.com/en-gb/media/press-releases/2015/gsk-announces-positive-new-data-comparing-incruse-ellipta-to-tiotropium-and-glycopyrronium-in-patients-with-copd/	on a margin of -50ml) or superiority of umeclidinium to tiotropium. Results Results from the randomised, blinded study 201316 showed that umeclidinium 62.5mcg once daily achieved a statistically significant improvement in lung function measured by trough forced expiratory volume in one second (FEV_1) at 12 weeks (P<0.001), compared to tiotropium 18mcg administered once daily. The difference in treatment effect observed was 59ml (95% CI: 29, 88) for umeclidinium compared to tiotropium based on a per protocol analysis. For the intention to treat population, the difference observed was 53ml (95% CI: 25, 81), which was also statistically significant (P<0.001). The most commonly reported on-treatment adverse events for both umeclidinium and tiotropium were headache (6% umeclidinium; 6% tiotropium) and nasopharyngitis (5% umeclidinium; 5% tiotropium). The overall incidence of on-treatment adverse events was 32% in the umeclidinium group and 30% in the tiotropium group. The incidence of any on-treatment serious adverse event in both treatment arms was 3%. Study Design Umeclidinium vs glycopyrronium (study 201315) This was a 12 week, multicentre, non-US, randomised, open-label study involving 1,352 patients, designed to compare the efficacy and safety of umeclidinium (62.5mcg once daily) administered via the Ellipta inhaler to glycopyrronium (44mcg once daily) administered via the Breezhaler inhaler in subjects with COPD. Patients were randomised 1:1 to umeclidinium 62.5mcg inhalation powder or glycopyrronium 44mcg. The primary endpoint was change from baseline in trough FEV_1 at Day 85. The primary analysis was to determine non-inferiority (based on a margin of -50ml) or superiority of umeclidinium to glycopyrronium. Results Results from the randomised, open-label study 201315 showed that umeclidinium 62.5mcg once daily was non-inferior to glycopyrronium 44mcg administered once daily, also measured by trough FEV_1 at 12 weeks. The difference in treatment effect observed was 24ml (95% CI: -5, 54) for umeclidinium compared to glycopyrronium based on a per protocol analysis. For the intention to treat population, the difference observed was 33ml (95% CI: 5, 61). The most commonly reported on-treatment adverse events for both umeclidinium and glycopyrronium were headache (8% umeclidinium; 10% glycopyrronium) and nasopharyngitis (8% umeclidinium; 8% glycopyrronium). The overall incidence of on-treatment adverse events was 37% in the umeclidinium group and 36% in the glycopyrronium group. The incidence of any on-treatment serious adverse event in both treatment arms was 3%.
ANORO	ERS Poster PA1001 Press release: 27th Sept 2015 http://www.gsk.com/en-gb/media/press-releases/2015/gsk-presents-post-	Data was presented at the European Respiratory Society (ERS) International Congress (poster PA1001), from an exploratory post-hoc analysis of phase III data, which showed that patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) who received *Anoro* (UMEC/VI 62.5/25mcg) had a reduced risk of experiencing a clinically important deterioration compared to tiotropium 18mcg or placebo over a 12-week treatment period.

	hoc-analysis-of-anoro-ellipta-data-assessing-markers-of-copd-deterioration-compared-to-tiotropium-or-placebo-using-a-novel-composite-endpoint/	Study Design This post-hoc analysis used a novel, composite endpoint, defined as a clinically important deterioration, to assess the effect of treatment on a number of factors that are each believed to represent a worsening of a patient's COPD. The analysis examined the time to a first clinically important deterioration which was determined by the occurrence of any of the following events: A decrease in lung function of ≥100 ml from baseline as measured by trough FEV_1; a deterioration in health-related quality of life defined as ≥4 unit increase from baseline in St George's Respiratory Questionnaire (SGRQ) total score; or the occurrence of an on-treatment moderate-to-severe COPD exacerbation. The post-hoc analysis examined data from four multicentre, randomised, blinded, parallel-group, 24-week trials: three comparing once-daily inhaled UMEC/VI 62.5/25mcg versus tiotropium 18mcg once daily (ZEP117115; DB2113360; DB2113374; data pooled into a single analysis) and one comparing once-daily inhaled UMEC/VI 62.5/25mcg to placebo (DB2113373). These four studies (ZEP117115; DB2113360; DB2113374; DB2113373) also included additional treatment arms however, these data were not included in the poster presented at ERS 2015. In the pooled analysis of ZEP117115, DB2113374 and DB2113360 trials, the intention to treat population (randomised and receiving at least one dose of study medication) comprised of 2,597 patients, 1,747 patients received either UMEC/VI 62.5/25mcg or tiotropium 18mcg. In the analysis of the DB2113373 study, the intention to treat population comprised of 1,532 patients, 693 patients received either UMEC/VI 62.5/25mcg or placebo. Results The results of the analysis showed that the risk of experiencing a clinically important deterioration was significantly lower for patients on UMEC/VI 62.5/25mcg once daily compared to tiotropium 18mcg once daily (hazard ratio: 0.62; 95% confidence interval [CI]: 0.54, 0.71; p<0.001) or placebo (hazard ratio: 0.37; 95% CI: 0.30, 0.45; p<0.001) in an intention to treat population, based on analysis of time to first deterioration. Conclusions This post-hoc analysis explored the potential impact of Anoro on disease deterioration. This is a new area of research and GSK will be conducting prospective studies to further evaluate these findings in the future. This is a novel concept which evaluates time to a first clinically important deterioration, and may in the future help our understanding of the factors which drive clinical stability in COPD, once more evidence accumulates on this concept.
INCRUSE BREO	Study 200109 clinicaltrials.gov identifier NCT01957163 Study 200110 clinicaltrials.gov identifier NCT02119286 Press release: 11 June 2014	Two phase III studies showed that patients with COPD who received the anticholinergic, Incruse (umeclidinium (UMEC) 62.5mcg), or umeclidinium 125mcg (an unlicensed dose) in addition to Breo (fluticasone furoate/vilanterol, "FF/VI"), an inhaled corticosteroid / long-acting $beta_2$-agonist combination, achieved an additional improvement in lung function (FEV_1) compared to patients receiving FF/VI plus placebo. Study Designs

	Siler TM et al. Respir Med 2015; 109(9):1155-63 http://www.gsk.com/en-gb/media/press-releases/2014/gsk-and-theravance-announce-positive-data-from-two-studies-evaluating-the-efficacy-and-safety-of-incruse-ellipta-when-added-to-relvarbreo-ellipta-in-patients-with-copd/	Both studies (200109 and 200110) were 12-week multicentre, randomised, double-blind placebo-controlled studies. 1238 patients with an established clinical history of COPD and an FEV_1 of ≤70%, were randomised and treated in the studies. Eligible patients were randomised 1:1:1 to receive UMEC 62.5mcg, UMEC 125mcg or placebo added to open-label FF/VI 100/25mcg. All treatments were administered once daily in the dry powder inhaler (DPI), Ellipta®. The primary endpoint for both studies was trough forced expiratory volume in one second (FEV_1) on Day 85. Results 200109: For the pre-specified primary endpoint of trough FEV_1 (Day 85), compared with placebo added to FF/VI 100/25mcg, both UMEC 62.5mcg and UMEC 125mcg added to FF/VI 100/25mcg, produced statistically significant improvements (UMEC 62.5mcg plus FF/VI 100/25 mcg: 124mL difference versus placebo plus FF/VI 100/25mcg; UMEC 125mcg plus FF/VI 100/25 mcg: 128mL difference versus placebo plus FF/VI 100/25mcg, both p<0.001). Incidence of on-treatment adverse events (AEs) were 36% UMEC 62.5mcg + FF/VI 100/25mcg, 39% UMEC 125mcg + FF/VI 100/25mcg, 35% placebo + FF/VI 100/25 mcg. The most frequently reported adverse events (greater than or equal to 3% in any treatment group) were headache, nasopharyngitis, back pain, dysgeusia (an abnormal taste or change in taste), cough, diarrhoea and influenza. The incidence of any cardiovascular adverse events of special interest was 2% UMEC 62.5mcg + FF/VI 100/25mcg, 1% UMEC 125mcg + FF/VI 100/25mcg, 3% placebo + FF/VI 100/25mcg. The incidence of pneumonia in the UMEC 125mcg + FF/VI 100/25mcg and the placebo + FF/VI 100/25mcg groups was 1%. There were no reported cases of pneumonia in the UMEC 62.5mcg + FF/VI 100/25mcg group. One death was reported in the placebo + FF/VI 100/25mcg group and was deemed non drug related by the investigator. There were no deaths reported in the UMEC + FF/VI 100/25mcg treatment groups. 200110: For the pre-specified primary endpoint of Trough FEV_1 (Day 85), compared with placebo added to FF/VI 100/25mcg, UMEC 62.5mcg and UMEC 125mcg added to FF/VI 100/25mcg, produced statistically significant improvements (UMEC 62.5mcg plus FF/VI 100/25 mcg: 122mL difference versus placebo plus FF/VI 100/25mcg; UMEC 125 mcg plus FF/VI 100/25 mcg: 111mL difference versus placebo plus FF/VI 100/25mcg, both p<0.001). Incidence of on-treatment adverse events (AEs) were 33% UMEC 62.5mcg + FF/VI 100/25mcg, 30% UMEC 125mcg + FF/VI 100/25mcg, 39% placebo + FF/VI 100/25mcg. The most frequently reported adverse events (greater than or equal to 3% in any treatment group) were nasopharyngitis, headache and back pain. The incidence of any cardiovascular adverse events of special interest was similar across treatment groups (<1% UMEC 62.5mcg + FF/VI 100/25mcg, 1% UMEC 125mcg + FF/VI 100/25mcg, 3% placebo + FF/VI 100/25mcg). The incidence of pneumonia was the same (<1%) in all treatment groups. Four deaths were reported in the placebo + FF/VI 100/25mcg group and one death was reported in the UMEC 62.5mcg + FF/VI 100/25mcg treatment group. All deaths were deemed non drug related by the investigator. Darrell Baker, SVP and Head, Global Respiratory Franchise, GSK said: "These data are an important addition to the evidence base supporting the efficacy and safety of Incruse. These studies are also the first to investigate the combined effect of two of the newest medicines from our respiratory portfolio,

		both of which provide 24 hour efficacy. We will continue to progress our research to expand our understanding of how the combined use of these medicines may provide physicians with another treatment approach to meet the individual needs of their patients."
ANORO SERETIDE/ ADVAIR	Study 116134 clinicaltrials.gov identifier NCT01822899 Singh D et al. BMC Pulmonary Medicine 2015; 15: 91 Study 114930 clinicaltrials.gov identifier NCT01817764 Study 114951 clinicaltrials.gov identifier NCT01879410 Donohue JF et al. Respiratory Medicine 2015; 109: 870-881 Press release: 14th March 2014 http://www.gsk.com/en-gb/media/press-releases/2014/gsk-and-theravance-announce-positive-results-from-studies-comparing-anoro-ellipta-with-seretide-diskus-and-advair-diskus-in-patients-with-copd/	Positive results from three phase III studies. Two studies comparing the efficacy and safety of the combination anticholinergic / long-acting beta$_2$-adrenergic agonist, *Anoro* (umeclidinium/vilanterol, 'UMEC/VI') with inhaled corticosteroid / long-acting beta$_2$-adrenergic agonist combination, Advair® (fluticasone propionate/salmeterol 'FSC 250/50') and the third comparing the efficacy and safety of Anoro with Seretide 'FSC 500/50' in patients with chronic obstructive pulmonary disease (COPD) and no history of moderate to severe COPD exacerbations in the last year. Study Designs All three studies (116134, 114930 and 114951) were 12-week multicentre, randomised, double-blind, double-dummy, parallel group studies. Approximately 2100 patients across the three studies, with post-salbutamol FEV1 of ≥ 30% and ≤ 70% and no history of moderate to severe COPD exacerbations in the last 12 months, were enrolled into the studies. Eligible patients were randomised to receive either UMEC/VI (62.5/25mcg) administered as a once-daily inhalation and placebo administered twice-daily, or FSC (500/50 mcg in study 116134 and 250/50mcg in studies 114930 and 114951) administered as a twice-daily inhalation and placebo administered once-daily. UMEC/VI was administered in the dry powder inhaler (DPI), *Ellipta* and FSC in the multi-dose powdered inhaler, Diskus. Results 116134: For the pre-specified primary endpoint of 0-24 h wm FEV_1 at the end of the treatment period (day 84), UMEC/VI 62.5/25mcg showed a statistically significant improvement of 80mL compared with FSC 500/50mcg (95% CI 46, 113; p<0.001). In this study, the most frequently reported (greater than or equal to 3% in any treatment group) adverse events were headache (9% UMEC/VI and 7% FSC), nasopharyngitis (3% UMEC/VI and 3% FSC), back pain (2% UMEC/VI and 3% FSC) and dysphonia (<1% UMEC/VI and 3% FSC). The incidence of any cardiovascular adverse events of special interest was similar in the two treatment groups (2% UMEC/VI and <1 % FSC). There was no incidence of pneumonia in the UMEC/VI group and <1% in the FSC group. The incidence of lower respiratory tract infections excluding pneumonia was <1% in the UMEC/VI group and none in the FSC group. The incidence of on-treatment non-fatal serious adverse events (SAEs) was similar across the treatment groups (2% in the UMEC/VI group and <1% in the FSC group). There was one patient with an on-treatment fatal SAE in the UMEC/VI treatment group and none in the FSC group. 114930: For the pre-specified primary endpoint of 0-24 h wm FEV_1 at the end of the treatment period (day 84), UMEC/VI 62.5/25mcg showed a statistically significant improvement of 74mL compared with FSC 250/50mcg (95% CI 38, 110; p<0.001). In this study, the most frequently reported (greater than or equal to 3% in any treatment group) adverse events were headache (7% UMEC/VI and 5% FSC) and nasopharyngitis (5% UMEC/VI and 2% FSC). The incidence of any

		cardiovascular adverse events of special interest was similar across the treatment groups (1% UMEC/VI and 2% FSC). The incidence of pneumonia was similar across both treatment groups (<1% UMEC/VI and 1% FSC). The incidence of lower respiratory tract infections excluding pneumonia was none in the UMEC/VI group and <1% FSC group. The incidence of on-treatment non-fatal serious adverse events (SAEs) was 2% in the UMEC/VI group and 3% in the FSC group. There was one patient with an on-treatment fatal SAE in the FSC group and none in the UMEC/VI group. 114951: For the pre-specified primary endpoint of 0-24 h wm FEV_1 at the end of the treatment period (day 84), UMEC/VI 62.5/25mcg showed a statistically significant improvement of 101mL compared with FSC 250/50mcg (95% CI 63, 139; p<0.001). In this study, the most frequently reported (greater than or equal to 3% in any treatment group) adverse events were headache (7% UMEC/VI and 7% FSC) and nasopharyngitis (4% UMEC/VI and 2% FSC). The incidence of any cardiovascular events of special interest was 3% UMEC/VI and 2% FSC. The incidence of pneumonia was <1% UMEC/VI and 1% FSC. The incidence of lower respiratory tract infections excluding pneumonia was <1% UMEC/VI and <1% FSC. The incidence of on-treatment non-fatal serious adverse events (SAEs) was 3% UMEC/VI group and 3% FSC group. There were 2 patients with on treatment fatal SAEs in the UMEC/VI group and 3 patients with on treatment fatal SAEs in the FSC group.

The clinical data presented above, not yet considered by the PBAC, confirms the place of GSK supported products in the current treatment paradigm. Feldman et al validates the use of UMEC as an effective monotherapy LAMA treatment when compared to tiotropium. The SUMMIT study provides long term safety and efficacy data for *Breo* and further enhances our understanding of the interplay between COPD and CVD. Singh et al confirms the appropriate place for LAMA/LABA therapy in COPD patients with no history of moderate-severe exacerbations.

The use of an open triple therapy combination (FF/VI plus UMEC) was assessed in two head-to-head studies versus dual therapy (FF/VI plus placebo), demonstrating clinical superiority (FEV1 improvement of 128mL, p<0.001) in this patient group without increased safety concerns, and providing the impetus for evaluation of a closed triple therapy in future trials, as presented below.

Table 3 - Emerging evidence exploring the use of 'closed triple' combination therapy

Study Name/ID/Publication	Details of study
IMPACT clinicaltrials.gov identifier NCT02164513 Press release:16th July 2014 http://www.gsk.com/en-gb/media/press-releases/2014/gsk-and-theravance-announce-initiation-of-phase-iii-programme-with-fixed-dose-triple-combination-treatment-ffumecvi-in-patients-with-copd/	Global phase III study, known as IMPACT, to evaluate the efficacy and safety of the 'closed' triple combination of FF/UMEC/VI in patients with COPD. IMPACT is the first pivotal phase III study in a programme to evaluate a once-daily closed triple combination treatment of an inhaled corticosteroid (ICS); a long-acting muscarinic antagonist (LAMA); and a long-acting $beta_2$-adrenergic agonist (LABA) in patients with COPD. Study Design IMPACT (InforMing the PAthway of COPD Treatment) is a double-blind, three-arm, parallel group study enrolling a total of 10,000 patients across 38 countries. Eligible patients will be randomised to receive either FF/UMEC/VI 100/62.5/25mcg, FF/VI 100/25mcg or UMEC/VI 62.5/25mcg once-daily for a period of 52 weeks. The co-primary endpoints of the study are: the annual rate of moderate and severe

	exacerbations comparing FF/UMEC/VI with FF/VI; and the annual rate of moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI. Key secondary endpoints include baseline changes in lung function (trough FEV1) comparing FF/UMEC/VI and FF/VI; time to first moderate or severe exacerbation in all three arms of the study; and the annual rate of severe exacerbations in all three arms of the study. Dave Allen, Head, GSK Respiratory Therapy Area Unit, R&D, said: "When developing our respiratory portfolio we recognised the need to offer a range of molecules that could be co-formulated in different combinations to meet the needs of individual patients. We know from the scientific literature and prescribing data that there are already COPD patients who receive three medicines in different inhalers, for whom a once-daily treatment in a single 'closed' device could be valuable. The IMPACT study will be important in advancing our understanding of how the combination of FF/UMEC/VI could be used in this setting when compared to dual combination therapy options." Rick E Winningham, Chief Executive Officer of Theravance, said: "The start of the IMPACT study marks a significant milestone in our development programme with GSK and we are excited about the potential opportunity for a triple combination treatment approach. This phase III programme has the potential to demonstrate the safety and efficacy profile of a new and important therapy that could deliver additional benefits and convenience to the growing number of adults living with COPD worldwide."
FULFIL clinicaltrials.gov identifier NCT02345161 Press release: 9th Feb 2015 http://www.gsk.com/en-gb/media/press-releases/2015/gsk-and-theravance-announce-start-of-phase-iii-lung-function-study-with-closed-triple-combination-treatment-ffumecvi-for-copd/	Second global phase III study to evaluate the effects of the investigational once-daily closed triple combination of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in patients with COPD. Study Design FULFIL (Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy) is a randomised, double-blind, double-dummy, parallel group multicentre study evaluating once-daily FF/UMEC/VI (100mcg/62.5mcg/25mcg) inhalation powder versus twice-daily budesonide/formoterol (400mcg/12mcg). The study aims to enrol 1,800 patients across approximately 180 study centres globally. The co-primary endpoints are: to evaluate the effects of FF/UMEC/VI on lung function and health related quality of life compared with budesonide/formoterol after 24 weeks of treatment. Other endpoints include the effect of FF/UMEC/VI on the annual rate of exacerbations compared with budesonide/formoterol, and the safety profile of FF/UMEC/VI compared with budesonide/formoterol over 24 weeks and 52 weeks of treatment. To provide additional longer term safety data, a sub-set of approximately 400 patients will remain on blinded study treatment for up to a total of 52 weeks. Patient perspectives of efficacy and physical activity will also be evaluated versus budesonide/formoterol. Dave Allen, Head, GSK Respiratory Therapy Area Unit, R&D, said: "Triple combination therapy is already a reality for one in three patients with COPD and is often dispensed in different inhalers with differing doses. By providing all three medicine components in a single inhaler we hope to offer more convenient dosing to patients, reduce the risk of exacerbation compared to dual therapy and, as a result, contribute to the improved management of their disease. Michael W. Aguiar, Chief Executive Officer of Theravance, added: "With FULFIL, we

	hope to demonstrate that a once-daily triple combination can reduce exacerbations in patients with COPD and deliver meaningful improvements in lung function and health related quality of life. If successful, a once-daily triple combination would be an important addition to our portfolio of combination respiratory products partnered with GSK including Breo and Anoro."

Conclusion

In conclusion, the evidence summarised above provides further support for the safety and efficacy of GSK medicines for COPD, adding to the existing body of evidence available and supporting clinicians making evidence-based treatment decisions.

GSK is continuing to lead the scientific debate by investing in new data generation. As the market and treatment paradigms have evolved to integrate the use of triple combination therapy, studies such as FULFIL and IMPACT have been designed to provide robust evidence in the future to enable reimbursement bodies such as the PBAC to comprehensively evaluate the cost-effectiveness of this treatment option.

4. ***Review the published literature on the safety of prolonged ICS use in monotherapy and in combination with LABA and/or LAMA for COPD that PBAC has not previously considered.***

The risk of pneumonia associated with the use of ICS or ICS/LABA will be the focus of GSK's response to TOR 4, with consideration and review of evidence that the PBAC has not previously reviewed. The evidence is summarised below in further detail.

The risks of pneumonia are well documented as evidenced by the COPD-X Concise Guide for Primary Care 'There is evidence for an increased risk of pneumonia for patients treated with ICS + LABA, however safety concerns should be balanced against the benefits of reduced rate of exacerbations and reduced decline in QOL' (Kew et al., Cochrane 2014)

The 2016 EMA Pharmacovigilance Risk Assessment Committee (PRAC) review of the risk of pneumonia with ICS containing medicines when used to treat COPD confirms that COPD patients treated with ICS are at increased risk of pneumonia; however the Committee's view is that the benefits of ICS continue to outweigh their risks (EMA, 2016).

- The PRAC looked at whether there were any differences in the risk of pneumonia between the products, and did not find conclusive evidence of such difference. Pneumonia remains a common side effect for all ICS containing therapies (beclomethasone, budesonide, flunisolide, fluticasone propionate and fluticasone furoate are corticosteroids authorised and marketed in the EU as inhalation formulations for use in COPD).
- An update of the product information is being recommended to adequately reflect the current knowledge. There is no change to the way these medicines should be used; however, doctors and patients should be vigilant for signs and symptoms of pneumonia in patients with COPD as the clinical features of pneumonia overlap with those of exacerbations of the underlying disease.
- The PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion. The review was initiated at the request of the European Commission on 7th May 2015, under Article 31 of Directive 2001/83/EC.

The recent Kew et al Cochrane review specifically addressing this subject matter, 'Inhaled steroids and risk of pneumonia for COPD' (Kew et al., 2014), represents the highest quality evidence currently available:

- The review included parallel-group RCTs of at least 12 weeks duration. Studies were included if they compared the ICS budesonide or fluticasone propionate/fluticasone furoate (grouped as 'fluticasone' for the purposes of the report) versus placebo, or either ICS in combination with a LABA versus the same LABA monotherapy for people with COPD.
- Cochrane identified 43 studies that met the inclusion criteria and more evidence was provided for fluticasone (26 studies; n=21,247) than for budesonide (17 studies; n=10,150). The populations within studies were more often male with a mean age of around 63, mean pack-years smoked over 40 and mean FEV1<50% (severe COPD).
- 'Fluticasone' increased non-fatal serious adverse pneumonia events (requiring hospital admission) (odds ratio (OR) 1.78, 95% CI 1.50-2.12; 18 more per 1000 treated over 18 month; high quality), and delivering it in combination with LABA, different doses, trial duration or baseline severity did not significantly affect the estimate. Budesonide also increased non-fatal serious adverse pneumonia events compared with placebo, but the effect was less precise and was based on shorter trials and fewer people (OR 1.62, 95% CI 1.00-2.62; 6 more per 1000 treated over 9 months; moderate quality). Moderate ratings reflect some uncertainty in the findings. Some of the variations in the budesonide data could be explained by a significant difference between the two commonly used doses.
- An indirect comparison of budesonide versus fluticasone monotherapy revealed no significant differences with respect to serious AEs (pneumonia related or all-cause) or mortality. No significant difference in overall mortality rates was observed between either of the inhaled steroids and the control interventions (both high quality evidence), and pneumonia-related deaths were too few to permit conclusions to be drawn.

- It reiterates that ICS medicines have proven benefits for people with repeated exacerbations and that they are commonly used as combination inhalers with LABA to reduce exacerbation rates and all-cause mortality, and to improve lung function and quality of life. Conclusions reached by the review are that ICS have been associated with increased risk of pneumonia, however the magnitude of risk is unclear and current evidence does not suggest any major differences in pneumonia between available combinations. The safety concerns highlighted must be balanced with established evidence of efficacy regarding exacerbations.

Ianella H et al., 2016 conducted a review of newly available data including assessment of several RCTs, meta-analyses and observational studies pertaining to the risk of pneumonia associated with the long term use of ICS in COPD. The review asserts that there is a considerable amount of evidence supporting the possibility of an increased risk, however, as yet, no statistically significant increase in pneumonia related 30-day mortality has been demonstrated.

- It explains that the lack of objective pneumonia definitions and radiological confirmations have been a major source of bias in clinical studies, because of the similarities in clinical presentation between pneumonia and acute exacerbations of COPD.
- Newer studies were not able to rule out budesonide as responsible for pneumonia, as previous evidence suggested, and there is still a need for evidence from head-to-head comparisons in order to better assess possible intra-class differences.
- Given that COPD represents such a complex and heterogeneous disease, it says attempts are being made to identify clinical phenotypes with clear therapeutic implications, in order to optimise the pharmacological treatment of COPD and avoid the indiscriminate use of ICS.

As previously alluded to in the response to TOR 3, newly available evidence provides further support for the safety profile of ICS/LABA therapies:

- The SUMMIT trial (Study to Understand Mortality and Morbidity in COPD) also provides additional data regarding the risk of pneumonia in patients taking *Breo* (ICS/LABA). Pneumonia was reported as an AE by 5% of patients in the *Breo* treatment group versus 4.6% in the placebo group. Furthermore, the incidence of pneumonia and serious pneumonia, respectively, was 5.7% *Breo*/ 5.2% placebo and 3.4% *Breo*/3.1% placebo. Therefore, SUMMIT provides additional confidence in the safety of *Breo* in a real world COPD population.
- In 'open triple' combination therapy trials 200109 and 200110, the incidence of pneumonia was investigated as an adverse event of special interest. In study 200109, the incidence of pneumonia in the UMEC 125mcg + FF/VI and the placebo + FF/VI groups was 1%. There were no reported cases of pneumonia in the UMEC 62.5mcg + FF/VI group. In study 200110, the incidence of pneumonia was the same (<1%) in all treatment groups.

Conclusion

From the information outlined above, it is acknowledged that there is an increased risk of pneumonia associated with prolonged use of ICS in COPD patients, however no parallel increase in mortality could be demonstrated. Newly available evidence is consistent with previous PBAC opinion in that the findings suggest a 'class effect' (*Breo* Public Summary Document (PSD) July 2014), as noted 'increased risk of pneumonia with ICS preparations is not exclusive to FF/VI, but applies to all ICS/LABA presentations'. Also the signs and symptoms of pneumonia in COPD patients may be initially indistinguishable from those of an exacerbation. ICS/LABA associated pneumonia risk should be considered within the context of potential benefit and should be reserved for the treatment of patients in which the risk/benefit profile of increased pneumonia is off-set by a reduction in exacerbations.

ICS/LABA represents a well defined treatment option for COPD patients with a history of repeated exacerbations. GSK is committed to ensuring that its ICS/LABA supported products (*Breo*, *Seretide*) are utilised in accordance with their TGA approved labels, PBS restrictions and current treatment guidelines.

Other safety concerns relating to prolonged use of ICS medicines, such as bone fractures and ocular effects, are not addressed in this response, however we recommend that the COPD-X guidelines are consulted, as any significant changes related to safety are integrated as part of the regular and timely review of the guidelines.

5. ***Analyse the current utilisation of PBS listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions.***

As an industry leader in promoting respiratory related QUM, GSK recognises that understanding the utilisation of our medicines is essential to meeting the evolving needs of our patients. GSK supports the use of high quality and robust data in order to evaluate the usage patterns of COPD treatments in Australia. As such, there are concerns regarding the limitations of the Medicare Australia data available for assessment of current utilisation.

There is no standardised approach agreed between the Government, Medicines Australia and other stakeholders when reviewing the utilisation data for PMRs. This results in a lack of consistency and transparency, limiting the ability of stakeholders to provide informative feedback. GSK supports collaboration between the Government and Medicines Australia in working towards a streamlined and improved data sharing framework for evaluation of medicines in PMRs.

Data limitations

GSK has a number of concerns regarding the methodology available for accurately identifying and assessing COPD patients within the dataset available and interpreting the extent of use of relevant PBS listed treatments.

The process by which a COPD patient is identified from available PBS utilisation data is highly uncertain. Identifying a patient based solely on treatment usage does not consider a number of confounding factors. Hence variability in the criteria used to segment this patient group results in highly varied results and makes it extremely difficult to draw any robust conclusions from the data.

For the purposes of this review, there is a significant risk that patients with asthma may be misclassified as COPD and vice versa. While there is some debate in the scientific community regarding the proportion of patients with both asthma and COPD (commonly referred to as ACOS), Australian estimates range from 15-23% (PSD *Breo* 2014, PSD *Onbrez* 2011) and global estimates range from 10- 50+% (asthmahandbook.org.au). As these patients may be eligible for asthma treatments, but classified as COPD patients, this poses another source of error in identifying appropriate COPD patients based on utilisation. There is extensive use of OTC SABA treatments (i.e. salbutamol) in patients with respiratory conditions, which will not be captured within this data source. Previous Drug Utilisation Sub-Committee (DUSC) reports have indicated that respiratory treatments may also be used for indications outside of those PBS listed (e.g. bronchitis), which further complicates the data analysis. This highlights the need for government to appropriately match utilisation with epidemiological data to fully understand the utilisation trends.

Not only is it difficult to accurately identify which patients are COPD patients, it is also problematic when attempting to assess the movement of patients between therapeutic interventions. The definition of 'switch' and 'add-on' is critical to understand the flow of patients between interventions and whether these transitions are aligned with treatment guidelines and PBS restrictions. If shorter cut off timelines are chosen, it will result in an overestimation of switch patients, and vice versa for add-in patients. Most critically, these definitions may either mask or exacerbate QUM issues that should be addressed for the benefit of Australian patients.

Other limitations of the data include: the clinical indication or nature of the condition for which the medication was prescribed is unknown (FEV1 for example is not recorded), data do not provide information on prescriptions written by HCPs that are not filled by the patient, therefore making it difficult to understand the prescriber's intent, and although prescriptions may be filled by the patient, patients may not be completely adherent to their therapy.

Data with significant limitations such as those identified above therefore does not represent a reliable platform from which accurate qualitative decision making can occur.

Clinical Guidelines

GSK considers the relevant COPD treatment guidelines in Australia to be the COPD-X and the GOLD guidelines (as per the response to TOR 1). Both of these guidelines have been accepted by the PBAC (PBAC PSDs for *Breo 2014*, *Onbrez 2011*), and they form the backbone of recommendations made in other clinical guidelines such as the Respiratory Therapeutic Guidelines.

In order to assess whether utilisation is consistent with these guidelines, the PBAC is required to consider the status of a patients' disease. In the guidelines, treatment recommendations are made based on the patient's clinical needs and the goal of therapy; prevention of exacerbations or symptomatic treatment (as per response to TOR 1). In order to understand the appropriateness of utilisation of COPD medicines with respect to treatment guidelines, available epidemiological data will need to be sourced and considered. Without availability of accurate data identifying the proportion of patients presenting to clinicians in each GOLD diagnostic category, the appropriateness of treatment utilisation is difficult to assess within the context of the guidelines.

Both GOLD and COPD-X guidelines support the use of triple therapy (ICS/LABA + LAMA) for the appropriate patient, for either treatment initiation or as a 'step-up' treatment option.

PBS restrictions

The PBS restrictions of GSKs medicines are provided in Appendix 1 for *Seretide* (fluticasone propionate with salmeterol xinafoate), *Breo* (fluticasone furoate with vilanterol), *Anoro* (umeclidinium with vilanterol) and *Incruse* (umeclidinium). The PBS restrictions do not preclude the use of dual or triple combination treatment, which is consistent with the current treatment guidelines (COPD-X and GOLD), recommending this treatment option for appropriate patients.

Extent of co-prescribing and utilisation within PBS restrictions and/or guidelines

Of the Medicare Australia subset data available to GSK (albeit limited), there appears to be substantial co-prescribing of medicines occurring for patients with COPD. This usage is reflected in the treatment guidelines, with treatment (mono, dual or triple therapy) selected based on adequate control being achieved. The data presents a broadly acceptable pattern of usage for patients. For patients on dual therapy, most of the combinations are represented by ICS/LABA and LAMA/LABA usage. There is a significant body of evidence supporting the safe and effective use of these combinations, reflective of inclusion of these products on the ARTG and PBS. It is evident from the previous DUSC review, however, that some usage of inappropriate combinations may be occurring. GSK is supportive of QUM initiatives to reduce inappropriate prescribing of multiple products and inadvertent improper poly-pharmacy, and has endorsed and provided funding to NPS programmes targeting COPD (detailed in response to TOR 6).

The prescribing and co-prescribing patterns for *Breo* and *Seretide* fit appropriately within guideline recommendations for ICS/LABA products. This is consistent with anecdotal discussions with prescribers, and is congruent with the products being available on the market for many years. The usage of *Incruse*, a monotherapy LAMA, is also well understood.

There is diversity, however, in the prescribing patterns for LAMA/LABA FDC products. While the majority of their use, based on the limited Medicare Australia data sample, is appropriate as 2nd line therapy, there is wide variation in how prescribers are using these treatments. There is considerable use stepped up/down from appropriate therapies such as a switch from LABA + LAMA, or a switch from triple therapy, respectively, consistent with the PBS restriction. However there may also be stepwise use from a variety of other combinations, which although are adherent with treatment guidelines, may not be within PBS restriction.

As per the response to TOR 1, GSK do not believe the PBS restriction for *Anoro*, a LABA/LAMA combination, appropriately represents its intended place in therapy and hence propose that the PBAC consider a change to the *Anoro* restriction (as discussed in further detail below).

Change to the PBS restriction for *Anoro Ellipta*

GSK has recognised and is concerned that *Anoro* is currently being underutilised in clinical practice due to the limitations imposed by its PBS restriction. Further, the mismatch between the PBS restriction and clinical

guidelines seems to be causing confusion with prescribers not certain of its clinical utility or where it's appropriate clinical place lies within the treatment paradigm.

Currently the PBS restriction for *Anoro* limits its use to second-line treatment for COPD patients who must have been stabilised on a combination of LABA and LAMA. This product is not PBS indicated for the initiation of bronchodilator therapy in COPD. Within the definitive treatment guidelines, patients who present in 'Group B' as defined by GOLD having more significant symptoms but a low risk of exacerbations, are recognised as appropriate patients to initiate on a LAMA or LABA or alternatively LABA/LAMA treatment (for patients with severe breathlessness).

The COPD-X guidelines allow use of LABA/LAMA as a treatment option for symptomatic patients 'For patients receiving SABAs, who have persistent troublesome dyspnoea, add a LABA or LAMA (or both in combination if monotherapy is not adequate) for regular use'. No mention is made of stabilising on both monotherapies before initiating LAMA/LABA combination therapy.

Additionally, the TGA indication does not state that patients must be stabilised on LAMA and LABA monotherapies prior to use, '*Anoro Ellipta is indicated as a long term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD*'.

A change to the Authority Required (Streamlined) benefit for fixed dose combination LABA/LAMA inhalers including *Anoro* is therefore proposed (see additional bolded text):

'Patients must have symptoms that persist despite regular bronchodilator treatment with a long acting muscarinic antagonist or long acting beta2 agonist; OR
Patients must have been stabilised on a combination of long-acting muscarinic antagonist and long-acting beta2-agonist'

The rationale for the requested change to the PBS restriction is addressed below:

Clinically appropriate initiation
The PBAC's concern that patients could be initiated on a FDC earlier than clinically appropriate without the adequate titration of individual components is addressed in the proposed restriction, ensuring that patients only commence treatment with LABA/LAMAs when they have persistent symptoms on LAMA or LABA monotherapy, OR if they are using a LAMA and LABA in separate inhalers. This is consistent with therapeutic treatment guidelines (COPD-X, 2015; GOLD, 2016) and approved TGA listings.

Patient compliance
Patient compliance in COPD is essential to optimise disease management. Suboptimal compliance is common among COPD patients with research demonstrating an inverse relationship to the number of medications taken by the patient (Lareau & Yawn, 2010). Simplifying the complexity associated with COPD medication is therefore essential to improving patient compliance and indeed health outcomes (Chrischilles et al., 2002). This is particularly relevant given that COPD-X guidelines indicate that up to 90% of patients don't use devices correctly. Based on findings such as these, clinical expert group, the TSANZ importantly have indicated that 'the fewer inhaler devices used the better as technique errors greatly limit effectiveness. Therefore, patients who are using both a LABA and a LAMA, a combination product is preferred over the mono-components in separate inhalers'. Furthermore, the Respiratory Therapeutic Guidelines (version 5, 2015) also allude to this fact 'If combination therapy with a LABA/LAMA is indicated, a FDC may be more convenient for patients rather than separate single-drug inhalers if a suitable combination is available.'

Furthermore, it is common for COPD patients to have other co-morbidities and hence their use of multiple medications for other concomitant conditions adds to the administration burden and complexity of polypharmacy.

Cost

One of the major concerns of the PBAC during the evaluation of the *Anoro* submission was the cost implication associated with patients initiating the FDC earlier than clinically appropriate, without the adequate titration of individual components.

GSK believes that the restriction proposed by the PBAC contradicts this concern, by promoting the use of a more expensive treatment alternative. The price of *Anoro (DPMQ = $91.89)* is significantly less than the cost of a LAMA and LABA *(DPMQ of Spiriva* and *Onbrez = $120.05)* in separate devices.

Further, promoting the use of two separate inhaler devices prior to initiation of the FDC has cost implications to patients, where they are required to pay for two separate co-payments versus one. It also has cost implications in terms of GP visits, where it may be necessary for the patient to attend the GP clinic on an additional occasion to obtain a script for the FDC upon stabilisation of a LAMA and LABA.

It is important to contextualise this increased cost in terms of the patient population affected. COPD patients are typically older and are characterised by multiple co-morbid conditions. In fact, it has been demonstrated that the average number of medicines prescribed to a COPD patient may be as high as 6.26 (Restrepo et al., 2008). Given that COPD prevalence increases with age, patients typically have limited earning capacity. Specifying a restriction that increases the cost to patients may therefore adversely impact treatment compliance and resultant health outcomes. It will ultimately adversely impact patient's access to the most effective medicines for treating their medical condition, as demonstrated in its under-utilisation.

Recent modification to FDC ICS/LABA PBS restriction in asthma

As part of the recent paediatric asthma PMR, the PBAC agreed to remove the PBS restriction for FDC ICS/LABA that required patients to be stabilised on concomitant ICS and LABA inhalers prior to commencing the FDC. This recommendation was made in line with National Asthma Council (NAC) guidelines, which no longer recommended stabilising patients on single product inhalers before adding LABA to ICS.

Current Australian and global COPD guidelines also do not recommend stabilising on concomitant inhalers when adding LAMA to LABA (COPD-X, 2015; GOLD, 2016). This is supported by the TSANZ who state that 'a combination product is preferred over the same products in separate inhalers'. Amending the LABA/LAMA restriction would be consistent with the recent modification to FDC ICS/LABA prescribing in asthma, which aligned its use with current treatment guidance and clinical expert advice.

Listing of alternative FDCs on the PBS

The PBS listing of FDC LABA/LAMA is inconsistent with the listing of alternative FDC products listed on the PBS, where it is commonly specified that a patient is eligible for the FDC if symptomatic after use of only one mono-component. This is the case for FDCs listed for the treatment of diabetes, cardiovascular disease and elevated intraocular pressure.

Conclusion

There are significant limitations in the Medicare Australia data available for COPD medicines. The most rudimentary limitation is the difficulty in correctly defining and identifying a COPD patient; which may be further complicated by the inadvertent inclusion of asthma and ACOS patients in any analysis. The crossover of asthma and COPD represents another interpretive issue, as these patients are treated using a different paradigm. OTC medications play a large part in the management of respiratory conditions, and the inability to capture the extent of OTC salbutamol use creates further complexity when assessing the appropriate use of medicines. The definitions used for initiation, switch or add-in treatment will have a significant effect on the data outputs and therefore the PBAC should consider this uncertainty in conjunction with the other confounding factors when interpreting this data.

There seems to be extensive co-prescribing occurring of COPD treatments, as identified in the DUSC review. This alone is no cause for alarm; both the PBS restrictions and the treatment guidelines do not preclude the use of dual or triple therapy in appropriate combinations. There remains an appropriate place in therapy for

LABA/LAMA and ICS/LABA dual combinations, or alternatively ICS/LABA/LAMA triple combinations in patients with uncontrolled disease. In response to the findings of the DUSC review, GSK supports initiatives to minimise the use of regimens containing multiple products in the same class of medication. With respect to LABA/LAMA product utilisation, amending the restriction to include step up from LABA or LAMA monotherapy (in accordance with current treatment guidelines and approved TGA listings) rather than switching from combined use of LABA and LAMA treatments in separate inhalers is warranted to provide further clarity of its appropriate place in therapy, alongside additional education of HCPs to improve patient outcomes.

6. ***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.***

The responses to TOR 1-4 support the continued safety and effectiveness of all GSK sponsored medicines included within the remit of this PMR. In regards to these COPD medicines, the PBAC has already established and accepted cost effectiveness through a robust evaluation process, recommending PBS listing on the basis of key efficacy and safety outcomes, which remain clinically relevant and valid. The treatment guidelines provide further support for the continued use of these medicines.
Government intervention to restrict the use of these products may adversely affect the armamentarium available to healthcare professionals to treat this severe and progressing condition.

The burden of COPD
Within the context of this PMR, it is critical that decisions are not made by Government to restrict PBS usage without understanding the implications considering the significant burden of COPD on the community, but rather a well-informed multifaceted evidence-based approach is encouraged exploring the return on investment of various QUM initiatives.

According to the Australian Institute of Health and Welfare (AIHW), COPD was the fifth leading cause of death in Australia in 2013 (AIHW 2016). In that year 6,462 people died from COPD (4.4% of all deaths). Currently, more than 1 in 20 Australians aged 55 and over have COPD (5.7%), including 29.2% of people aged 75 and over. As COPD is related to smoking, due to educational campaigns the burden has decreased over time as the smoking rate has declined. COPD mortality rates are higher for people living in more remote areas and for people living in areas of low socioeconomic status, with mortality rates being 2.5 times higher among Indigenous Australians. The burden on healthcare services is significant, with over 58,900 hospitalisations during 2013-14. This represents 6% of all hospitalisations in the >55 age group. The direct health expenditure attributed to COPD in Australia was estimated at $929 million in the 2008-09 financial year, consisting predominantly of admitted patient costs (57%), prescription medicines (23%) and out-of-hospital medical services (19%) (Lung Foundation, 2016). Of the financial costs, a large proportion is due to the loss of productivity, including lower employment, absenteeism and the workplace impact of premature death of Australians with COPD (Access Economics 2008). In the period 2011-2014, there has been a stabilisation (and recent reduction) in COPD hospitalisations (AIHW 2016). This reduction in hospitalisations coincides with the increased uptake and availability of medications in the community setting, and represents significant cost savings for government.

Any alterations to the accessibility of PBS treatments as a result of this PMR may have both equity and budgetary implications for the broader community.

Cost effectiveness of GSK products
The cost effectiveness of GSK medicines for COPD has already been established by a robust and structured PBAC process. The parameters in which cost effectiveness were established remain clinically relevant and appropriate for all GSK COPD products. The efficacy endpoints included in key clinical trials were improvements in lung function as measured by FEV1 (for *Seretide*, *Breo*, *Anoro* and *Incruse*), reductions in exacerbations (for *Seretide, Incruse* and *Breo*) and improvements in health related quality of life (all products). Emerging efficacy and safety information has been presented in the response to TOR 3 and 4 and further supports the existing body of evidence available for these products. There are no new safety signals which would warrant a re-evaluation of cost effectiveness.

GSK acknowledges that there are an increasing number of products available for COPD patients. Whilst this provides for greater choice of treatments for prescribers, unfortunately it creates confusion for prescribers and their patients and adds complexity to treatment regimens. Patients administering several different devices have an increased risk of inappropriate use of their medicines (Lareau & Lawn 2012, Chrischilles et al., 2002), with some COPD patients taking up to three different device types for their treatment. Further complexity is added with variations in the frequency of dosing medicines, with some devices taken once or twice a day. The portfolio of the latest GSK COPD medicines, (*Breo*, *Incruse* and *Anoro*), have been formulated as once daily treatments. Evidence suggests that using therapies once a day improves treatment compliance (Chrischilles et al., 2002).

These new medicines are available in the same device, *Ellipta*, which reduces complexity for patients with respect to mastering device technique and as a result have shown to be preferred by patients (Kirby et al., 2016). This offering allows the smooth transition between monotherapy LAMA or dual therapy ICS/LABA or LAMA/LABA, which enables the maximum benefits to be derived from treatment via improved compliance and reduced complexity. Currently, a 'closed' triple therapy option containing FF, VI and UMEC in the same *Ellipta* device is under investigation in clinical trials (IMPACT and FULFIL). GSK look forward to presenting the cost effectiveness of this medicine to the PBAC for evaluation in due course.

GSK supports the continued use of our medicines in COPD in accordance with treatment guidelines and PBS restrictions. A review of the PBS restriction for LABA/LAMA products would ensure consistency of guidelines and PBS restrictions. Based on the information presented in the response to TOR 5, GSK do not believe a cost-effectiveness review is justified.

GSKs current commitment to improving Quality Use of Medicines

GSK is committed to appropriate prescribing of COPD treatments. The LFA and respiratory companies took an action to develop additional educational resources and/or aids to assist clinicians to identify various COPD products by their class and avoid the prescribing of products from the same class. Given our commitment to the principles guiding the quality use of medicines, GSK has welcomed the prospect of working with the NPS to assist in appropriate prescribing for patients with COPD.

GSK has provided a significant unrestricted educational grant to the NPS for the development and implementation of a COPD education program. The aims of the educational activity is to provide greater clarity to GPs on medicine choices for COPD, improve adherence and inhaler technique, and reduce the confusion associated with the use of medicines for chronic airways disease. To achieve maximum health professional behaviour change, NPS MedicineWise will deliver a multi-faceted educational visiting program centred on a format of facilitated practice-based multidisciplinary meetings to 1,000 GPs around Australia in 2016. Small group meetings of this type have proven efficacy in achieving measurable and lasting impacts on prescribing behaviour, and are rated highly by health professionals in evaluations. The format of the sessions include an interactive group session facilitated by clinical service specialists who are trained to engage health professionals in high level peer-to-peer learning. The content of the sessions include recent guideline updates. These sessions will give health professionals the opportunity to compare and contrast medicines and treatments and ask questions of peers and facilitators. By framing education against guidelines, GPs feel confident they are providing up to date best practice care. The sessions will be supported by the new concise version of COPD Guidelines from the LFA. There will be particular focus on inhaler technique and adherence. Case studies will be used to highlight appropriate medicine choice and action plans will be developed by each participant with key take home actions for that individual. Resources provided include:

- Comparative medicine tables, with focus on easy reference
- Case studies
- Guideline summary
- Individual action plans

GSK recommendations to improve Quality Use of Medicines

GSK is strongly supportive of QUM initiatives to improve patient care and appropriate prescribing and insist that the PMR outputs predominantly focus on these measures to address any inconsistencies in prescribing practices and utilisation of medicines. In order for patients, Government and taxpayers to obtain full value from these medicines, improving QUM must be a priority for this PMR.

Any implications to the price of these COPD medicines as a result of revisiting cost-effectiveness, based on a review of the limited utilisation data, will not lead to improved outcomes for COPD patients. It is, however, in the interests of Australian patients, for Government to identify any inappropriate use of COPD medicines and address these concerns through QUM initiatives and targeted programmes. This can be facilitated through reputable independent organisations, such as the NPS, or through agreements with HCP groups, such as the

recent 6- CPA, which can leverage the use of pharmacy services to promote QUM. The following recommendations are proactively provided for consideration to improve the use of COPD medicines within the current cost-effectiveness framework.

- NPS programmes

The NPS have been highly successful in delivering QUM initiatives to prescribers and other healthcare professionals for several years. As such, GSK welcomed the recommendation of the PBAC for the NPS to address usage of COPD products (*Breo* PSD March 2014). As noted above, GSK contributes to a current NPS program aimed at educating healthcare professionals on the use of respiratory medications. It is our proposal that the NPS further drive and prioritise this activity. Some areas of focus may be to ensure patients are appropriately diagnosed with COPD through the use of spirometry, encouraging patients (and in particular the elderly) to present to primary care facilities when they are struggling with burdensome symptoms rather than dealing with the burden silently, minimising inappropriate co-administration of treatments by ensuring the treatment guidelines are followed and improving patient compliance and adherence through regular assessment of inhaler technique. With an increasing number of devices and treatment combinations available, such programmes will undoubtedly improve the utilisation of these treatments.

- NPS audit of prescribing patterns

NPS audits evaluating prescribing patterns have historically provided high quality data in which decisions on utilisation of treatments have been made. Only through the appraisal of quality data should assessment of treatment patterns, and therefore prescribing behaviour, be determined. As identified in the response to TOR 5, there are a number of limitations in the Medicare Australia PBS data. GSK is supportive of an NPS audit of this therapy area, with the goal of improving treatment utilisation.

- Review of the *LABA/LAMA* PBS restriction

The current PBS restriction for *Anoro* requires patients to be '*...stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist'.* The restriction does not promote the optimal use of this medicine and is not aligned with treatment guidelines in this respect. Amending the restriction for this product would align with evidence-based treatment guidelines, reducing the risk of inappropriate combinations being used and encouraging QUM (further detail included in response to TOR 5).

- Add alerts to prescribing software

Within the prescribing software platform, integration of alerts may provide a mechanism to address co-prescribing concerns during the consultation with a primary care physician. Alerts within the system provide a quality assurance step in the prescribing process which can reduce the risk of inappropriate poly-pharmacy occurring. GSK is unaware of any alerts currently available in the prescribing software which warn physicians when multiple inhalers of the same medicine class have been prescribed. It is our recommendation that providers of prescribing software are approached to improve QUM of COPD medicines at the point of prescribing.

- Add alerts to pharmacy dispensing software

Pharmacists are a key source of primary care advice due to their presence in the community, accessibility and extensive medicinal knowledge. At the point of dispensing, pharmacists are able to identify QUM issues for patients and this creates an opportunity for them to address inappropriate co-prescribing. GSK is unaware of any warnings currently available in the dispensing systems that alert pharmacists when medicines of the same medicine class are dispensed for COPD. It is our recommendation that providers of dispensing software are approached to incorporate this safety measure.

- Implement QUM pharmacy programmes; Utilisation of MedsCheck service & Management of Chronic illnesses

Pharmacy is suitably placed to play a greater role in the management of COPD patients. Given the nature of the concerns that have been highlighted in this PMR (complex prescribing practices, polypharmacy, treatment compliance issues pertaining to inappropriate inhaler technique, over-reliance of OTC SABA etc.) pharmacists are well equipped to provide relevant advice and assistance. In addition, the recently launched 6CPA provides

another opportunity to further enhance the value of the pharmacy service. The 6CPA includes provisions to increase the role of pharmacy in the management of chronic illness. As the burden of COPD is significant in Australia, it is appropriate for this condition to be added to the chronic illness list. This would ensure that COPD, and its complex disease management, is at the forefront of primary care initiatives.

Pharmacies are funded in the current pharmacy agreement to perform MedsCheck for eligible patients. MedsCheck is a Government funded in-pharmacy consultation service that reviews a patients use of medicines at the time of dispensing (PSA 2016). The current criteria require patients to be taking at least five medicines which is relevant for COPD patients as they are often on multiple medications for concomitant conditions. The MedsCheck framework should be explored to tackle QUM concerns with COPD medicines.

GSK also supports the Home Medication Review (HMR) program. This initiative provides a comprehensive review of patient's medications and general health, with a view to optimising treatment outcomes. As the HMR is conducted within a patient's home, it is a suitable program to support elderly COPD patients.

- E-health (myHealthRecord)

GSK welcomes the advent of the e-health medical record Government initiative. In the context of COPD, this project enables sharing of a patient's medical history between multiple prescribers, which facilitates improved oversight and reduces the risk of inappropriate prescribing.

- Enhancing smoking cessation programs

Smoking cessation programs have proven to be the most successful method for reducing the burden of COPD. It is proposed that smoking cessation programs continue to be a focus for COPD prevention.

Conclusion

The cost effectiveness of GSK sponsored COPD treatments have been accepted by the PBAC through a robust evaluation process and currently there is no justification to warrant a review. Additional safety and effectiveness data, published since the listing of these medicines, further supports the appropriate use of these products, with the risk/benefit profile remaining unchanged. Medicare Australia utilisation data for these medicines is difficult to interpret due to the significant limitations, however trends indicate that the place of ICS/LABA and monotherapy LAMA are well understood.

GSK however recommends that the PBS restriction for LAMA/LABA be reviewed to ensure clear alignment with treatment guidelines and its approved TGA indication. GSK advocates for a multi-faceted approach to address QUM concerns and has provided a number of recommendations for consideration. These initiatives ensure the full benefits of the medicines are realised, as intended by enabling access via the PBS.

Conclusion

As a robust and rigorous PBAC process underpins the evaluation and determination of cost effectiveness, GSK consider a re-assessment of cost-effectiveness to be unnecessary for the purposes of this PMR. Rather, GSK considers the core issue of this PMR to be QUM.

As a Sponsor of several important COPD medicines, GSK welcomes participation and stakeholder input into this PMR. We acknowledge the QUM concerns discussed by DUSC and appreciate the need to work with the PBAC and the Government to ensure that COPD patients are treated appropriately with the therapeutic armamentarium available today, in alignment with current treatment guidelines and best practice. GSK supports the appropriate use of its medicines.

GSK acknowledges the increasing complexity for physicians in managing COPD patients given the rapid advances in new medicine development, and will continue to provide comprehensive educational support to Australian healthcare professionals to ensure the appropriate use of its COPD medicines, consistent with both the registered and reimbursed indications and as supported by current treatment guidelines. The response herein explores potential ways for the broader COPD community to address key QUM concerns, including initiatives to enhance patient adherence to therapy and improve inhaler technique.

In addition, a revised PBS restriction for the LAMA/LABA combination product *Anoro*, is proposed, which aims to improve clarity around its clinical place in therapy and ensure appropriate alignment to treatment guidelines and the TGA listing.

GSK request that the outcomes from the PBAC deliberations relating to this PMR be discussed at a round table forum (stakeholder forum) before being implemented in order to provide context to the recommendations and ensure that the recommendations are medically and clinically sensible and practical.

GSK looks forward to a good number of its recommendations and views being considered and encourages further dialogue throughout the review.

Thank you for your consideration of this input.

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Appendix 1:

Seretide (fluticasone propionate/salmeterol) 500/50, Seretide (fluticasone propionate/salmeterol) 250/25, Breo (fluticasone furoate/vilanterol) 100/25 – Restricted benefit(s):

Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy AND the treatment must be for symptomatic treatment.

Notes: Patient must not be on a concomitant single agent long-acting beta-2 agonist. This product is not indicated for the initiation of bronchodilator therapy in COPD.

Anoro (umeclidium/vilanterol) 62.5/25 – Authority Required (Streamlined):

COPD: Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.

Note: This product is not PBS-subsidised for the treatment of asthma. This product is not indicated for the initiation of bronchodilator therapy in COPD. The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy. A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium. A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.

Incruse 62.5 (umeclidium) – Restricted benefit:

Note: COPD