National Essential Medicines List
Tertiary/Quaternary Medication Review Process

Date: October 2017

Medication: Long acting muscarinic antagonists (LAMA) e.g. Tiotropium or Glycopyrronium

Indication: Chronic Obstructive Pulmonary Disease (COPD) with following criteria:

- COPD confirmed by spirometry (a post-bronchodilator FEV/FVC <0.7 and an FEV1 of ≤50% predicted (Severe or very severe airflow limitation) (Equivalent to GOLD Categories C and D).
- COPD patients with a post-bronchodilator FEV/FVC <0.7 and an FEV1 of ≤70% predicted (moderate airflow limitation) and at breathlessness (effort limitation) associated with and impairing usual unhurried daily activities (domestic and/or work-related) (Equivalent to GOLD Category B).
- History of at least one moderate or severe exacerbation of COPD in the past year (worsening of symptoms of breathlessness, cough, and/or sputum quantity and/or colour change necessitating use of an antibiotic and/or short course of oral or systemic corticosteroids, with or without attendance for emergency care or hospitalization (Second criterion for GOLD Category D).

Executive summary:

Long Acting Muscarinic Antagonists (LAMA) such as tiotropium and glycopyrronium are used in the management of COPD[1]. They have been shown to improve lung function, quality of life and exercise tolerance. They have also been associated with reduced COPD-related exacerbations, associated hospitalisations and duration of hospital stay. Both the South African Thoracic Society (SATS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD), guidelines recommend the use of long acting anticholinergic drugs (or long acting beta agonists) in moderate to very severe disease as defined by lung function (FEV_1). The most up to date guideline, utilizing the GRADE methodology (European Respiratory Society guidelines of 2017), confirms their superiority over long acting β agonists (LABA) as monotherapy for COPD in that LAMA's have demonstrated greater efficacy in terms of exacerbation reduction, with similar safety profile.[2] These recommnedations are supported by published peer-reviewed evidence including individual papers and Cochrane reviews[7,8,9,10,11.]

At present, the EML does not make provision for an inhaled anticholinergic agent for the management of COPD. Ipratropium is ineffective in improving lung function or quality of life and has no effect on hospitalisation or exacerbations, and was subsequently removed from the EML. A LABA is available, however there is a need for a further agent for those patients who are uncontrolled.

Most evidence for the efficacy of a LAMA is from tiotropium. However, glycopyrronium, an alternative LAMA, has recently has become available on the market in South Africa. The published literature reflects that tiotropium and glycopyrronium are at least equivalent in terms of safety and clinical efficacy. There is also evidence for the value of the LAMA/LABA combination over a LABA alone. Except for defined subgroups of COPD patients, the use of LABA/LAMA combination rather than a LABA/Inhaled corticosteroid in severe COPD has also been found to be the preferred treatment approach.

Tiotropium and glycopyrronium are muscarinic M_3 receptor selective blocker with >24hrs duration of action. Thus they are anti-bronchoconstrictors, providing bronchoprotection when cholinergic tone is induced by noxious stimuli, whether atmospheric pollutants, weather changes, or respiratory tract infections – the most common causes of COPD exacerbations . Administration via the dry powder inhaler device has been shown to have a greater effect on lung function over 24 hours than either the twice daily administration of salmeterol, a long acting beta agonist or ipratropium. LAMA's are recommended for use in moderate to severe disease to reduce symptoms and exacerbations and arepreferred to inhaled corticosteroids for reducing exacerbations as they are not associated with important steroid side effects such as osteoporosis, skin changes and increased risk of TB or pneumonia. In addition, in patients not responding to a single agent, combination LABA /LAMA improves lung function more than either agent alone, reduces dyspnoea, and is the recommended option in patients in the B, C or D GOLD categories with the addition of corticosteroids in the most severe C or D categories.

Introduction:

According to the data of World Health Organization (WHO), there are 600 million COPD patients worldwide and every year 2.3 million people lose their lives due to COPD. *It is expected that COPD will take the 3rd place in death cases in 2020, while it was the 6th most common cause of death all over the world in 1990. COPD takes 11th place among the worldwide leading causes of Disability Adjusted Life Years (DALY) and it is estimated that it will reach to the 7th rank in 2030*.[1] Data from Cape Town estimates that the prevalence of COPD in adults could be as high as 22% for males and 17% for females (Buist, Lancet 2007; evidence from the BOLD Study performed in Ravensmead and Uitsig suburbs of Cape Town).[3] As smoking and tuberculosis (TB) are important additional risk factors for COPD in South Africa, the prevalence of COPD is high and expected to rise over the next few years.

COPD is associated with reduced quality of life and premature mortality, particularly when associated with exacerbations and hospital admission. Exacerbations are a major driver of chronic healthcare costs. Moderate to severe exacerbations results in emergency unit visits and hospitalisations. A number of international studies have shown the large costs associated with hospitalisation and medication in COPD patients.[4,5] In the USA, changing to more effective drug regimes has been predicted to reduce costs per COPD patient by nearly $1000.[6]

Short-acting β2 agonists and the anticholinergic (ipratropium), are recommended in early mild COPD, but in moderate to severe disease should be used only as-needed in addition to a long-acting bronchodilator. Inhaled corticosteroids (ICS) are only indicated in patients with frequent

exacerbations and severe disease as they have little, if any benefit on other outcomes (e.g symptoms and lung function), and use in COPD is associated with an increased risk of lower respiratory tract infections including pneumonia and pulmonary tuberculosis. It is thus inappropriate to use an ICS in mild/moderate COPD in South Africa. There are an increasing number of reports of an excess of active TB in COPD patients treated with ICS, presumed to be either reduced bronchial host defences, or reactivation resulting from the topical effects of powerful ICS with prolonged duration of action.

Search strategy:.

The search key words included COPD, Long acting muscarinic antagoniste, tiotropium, glycopyrronium bronchodilatation, exacerbations, COPD pharmacology in various combinations. There are several Cochrane reviews and the GOLD 2016 Strategy document summarises and updates global recommendations on a yearly basis.

Selection of studies:

No studies have been specifically excluded. The most up to date systematic reviews have been included over the key stand alone multicentre trials (both sponsored and independent).

Evidence synthesis:

A summary of the meta-analyses and key papers are presented here – for the primary comparison for tertiary approval usage – special focus on LAMA vs. formoterol and LAMA vs. LABA/ICS is presented.

Study description	Patient inclusion criteria	Interventions/Dose (no. of patients)	Primary outcome to assess clinical response	Results	Comments
Chong *et al* - Cochrane 2012[7]	Stable COPD patients	Tiotropium Vs LABA (Salmeterol/ formoterol/ indacaterol)	1. Quality of life (QoL) (using a validated COPD scale – St Georges) 2. Exacerbations – requiring short-burst oral corticosteroids and/or antibiotics **3.** Mortality – all cause	1. High level of heterogeneity – data could not be pooled for St George's Respiratory Questionnaire(SGRQ) QoL scores. 2. Reduced exacerbations OR 0.86 (95%CI 0.79-0.93) a. POET study (Vogelmeier NEJM 2011) ARR for exacerbations by 8% (NNT = 12.5) 3. No statistical difference in all-cause mortality. <u>Secondary outcomes:</u> • Reduced	Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall hospitalisation rates or mortality during the study periods.

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				exacerbations leading to hospitalization OR 0.87 (95%CI 0.77-0.99) • Was associated with fewer serious adverse events OR 0.88 (95% CI 0.78 - 0.99) • Was associated with less study withdrawals OR 0.89 (0.81- 0.99)	
Farne *et al* - Cochrane review 2015[8]		LABA Vs Tiotropium Vs Tiotropium plus LABA	1. Quality of life 2. Exacerbations 3. Symptoms 4. Lung function 5. Serious adverse events	<u>LABA vs Tiotropium plus LABA</u> 1. Small but significant improvement in SGRQ MD -1.25, (95% CI -2.14 to -0.37) 2. Reduction in exacerbation rate OR 0.80 (95% CI 0.69 to 0.93) 3. Improvement in FEV_1 MD 0.07, (95% CI	Small mean improvement in health-related quality of life and FEV1 for participants on a combination of tiotropium and LABA compared to either agent alone. In addition, adding tiotropium to LABA reduced

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				0.06 to 0.09)	exacerbations, although adding LABA to tiotropium did not. Hospital admission and mortality were not altered by adding LABA to tiotropium, although there may not be enough data.
FLAME Study NEJM 2016[9] **Randomised, double-dummy, noninferiority trial**	Patients with COPD and a high risk of exacerbations	LAMA/LABA (1680) combination compared to LABA/ICS (1682)	Annual rate of all COPD exacerbations	1. Reduced exacerbation rate with LAMA/LABA RR 0.89 (95%CI 0.83 to 0.96), p = 0.003 2. Lengthened time to first exacerbation 71 vs. 52 days (95%CI 46 to 57), HR 0.84 (95% CI 0.78 to 0.91), p < 0.001 3. Reduced pneumonia 3.2% vs. 4.8% p=0.02	Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year.
Cheyne *et al* -	Patients with	Tiotropium	1. Trough forced	1. Increased FEV_1 by	Tiotropium

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Cochrane review 2013[10]	stable COPD	Vs Ipratropium bromide	expiratory volume in one second (FEV1) at three months 2. All-cause non-fatal serious adverse events (SAEs) 3. Disease specific serious adverse events, if independently adjudicated	109 ml at 3 months (95% CI 81 to 137) 2. Fewer non-fatal serious adverse events with Tiotropium OR 0.5 (95% CI 0.34 to 0.73) 3. Reduced COPD related serious adverse events OR 0.59 (95% CI 0.41 to 0.85) 4. Reduced hospital admissions OR 0.34 (95% CI 0.15 to 0.7) 5. Reduced exacerbations OR 0.56 (95% CI 0.31 to 0.99) 6. Improved quality of life (single study) mean difference -3.3 (95% CI -5.63 to-0.97)	treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There was no significant difference in deaths between the two.
Karner *et al* - Cochrane review 2012[11]	Patients with COPD	Tiotropium Vs Placebo	1. Quality of life; measured with a scale validated for COPD, such as St George's Respiratory Questionnaire	1. Reduced exacerbation rate OR 0.78 (95% CI 0.7 -0.87) • Calculated number needed to treat=16	This review shows that tiotropium treatment was associated with a significant improvement in

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			(SGRQ), Chronic Respiratory Questionnaire (CRQ). 2. Exacerbations; requiring oral corticosteroids and/or antibiotics. 3. Mortality; all-cause. 4. Hospital admissions; all-cause and due to exacerbations.	(95% CI 10 – 36) 2. Improved quality of life – mean difference -2.89 (95%CI -3.35 to -2.44) 3. Reduced hospitalization due to exacerbation OR 0.85 95CI 0.72 to 1.00) 4. Improved lung function by 118 ml (95% CI 113.07 – 124.77)	patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation.

Evidence quality:

Four Cochrane reviews were presented which included randomized controlled trials, where risk of bias assessed and reported generally as low. It however should be noted that sequence generation and allocation concealment was was often reported as unclear; and outcomes reported in the registered trial protocols differed from those reported in the final publication. Additionally funding bias existed with many studies funded by a pharmaceutical company and included authors on the trial employed by the drug manufacturer.

Therapeutic Class

The majority of the evidence focuses on Tiotropium. Glycopyrronium bromide however has been shown to have similar outcomes and safety profile to Tiotropium. The GLOW2 study randomized patients to glycopyrronium, placebo or open-label Tiotropium for 52 weeks. The primary outcome was trough FEV1 at 12 weeks. Trough FEV1 increased in both glycopyrronium as compared to placebo (95% CI 64.6–130.2; $p < 0.001$) and tiotropium (95% CI 45.6–121.4; $p < 0.001$).[12]

LAMA's are thus considered a therapeutic class for the tertiary EML.

Costs:

Product description	Price source	Product	Strength	Supplier	Price
Tiotropium Bromide	National contract HP07-2017DAI	Spiriva	18mcg	Ingelheim Pharmaceuticals (pty) Ltd	**R374.76**
Tiotropium bromide	Single exit price 27 May 2017	Spiriva	18mcg	Ingelheim Pharmaceuticals (Pty) Ltd	**R693.29**
Tiotropium bromide	Single exit price 27 May 2017	Spiriva Respimat	5mcg	Ingelheim Pharmaceuticals (Pty) Ltd	**R716.64**
Tiotropium bromide Refill	Single exit price 27 May 2017	Forvent	18 mcg	Ingelheim Pharmaceuticals (Pty) Ltd	**R412.69**
Tiotropium bromide Complete	Single exit price 27 May 2017	Forvent	18mcg	Ingelheim Pharmaceuticals (Pty) Ltd	**R455.25**
Glycopyrronium Bromide	Single exit price 27 May 2017	Seebri Breezhaler	50mcg	Novartis South Africa (Pty) Ltd	**R344.42**

Summary:

There is evidence in terms of reduction of exacerbations and hospitalisations, to support the use of LAMAs in the management of COPD at tertiary level. As a result there is merit in including a LAMA in the armamentarium of treatment approaches within the South African context.

Recommendation:

Based on the current price, it is not recommended that a LAMA be included on the Essential Medicines List for the maintenance treatment of COPD in the above outlined indication.

Review indicator:

Price similar to LABA/ICS

References

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