Application to add a
Long Acting Muscarinic Agent (LAMA) inhaler
to the Essential Medicines List
1. Summary statement of the proposal for inclusion

The successful control of COPD requires reliever and maintenance medicines, including bronchodilators that relax airway smooth muscle. Currently the WHO List of Essential Medicines for COPD contains two bronchodilators, salbutamol and ipratropium, both being short-acting in nature.

Bronchodilators (BD) are central to COPD treatment (GOLD 2019). They reduce symptoms, and risk and severity of exacerbations while also improving overall health status and exercise tolerance.

Two classes of BD are available; beta agonists and anti-muscarinics. Both are available in short and long acting formulations (Long acting beta agonists, LABA; long acting anti-muscarinics, LAMA) (Barnes 1995).

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle (Melani 2015). Long-acting antimuscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium bromide and umeclidinium have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.

There are data showing benefits of long over short acting formulations (eg tiotropium vs ipratropium) (van Noord, Bantje et al. 2000, Cheyne, Irvin-Sellers et al. 2013, Cheyne, Irvin-Sellers et al. 2015).

There is also evidence on the effectiveness of anti-muscarinics when compared with LABA agents (Appleton, Jones et al. 2006, Decramer, Chapman et al. 2013) (Vogelmeier, Hederer et al. 2011, Karner and Cates 2012).

As briefly discussed here, LAMA medications with prolonged bronchodilator effect are relevant and efficacious for the treatment of symptoms in moderate to severe COPD patients. It is thus proposed to add this formulation to the EML.

2. **Name of the WHO technical department supporting the application**
   Department of Non Communicable Diseases.

3. **Name of the organisation(s) consulted and/or supporting the application**

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   Contributors
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Montevideo, Uruguay
4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

**DIN (Drug Identification Number)**

02246793  SPIRIVA 18µG Capsule

**DIN (Drug Identification Number)**

02435381  Spiriva Respimat 2.5 µg Oral inhalation

**DIN (Drug Identification Number)**

02394936  Seebri 50 µg Capsule for inhalation

**DIN (Drug Identification Number)**

02423596  Incruse Ellipta 62.5 mg/blister

5. Formulations and strengths proposed for inclusion; including adult and paediatric

**Tiotropium**

Spiriva HandiHaler, Spiriva Respimat (Boehringer Ingelheim)

**Adults**

capsule (Spiriva HandiHaler; powder for oral inhalation)

- 18mcg  
  solution for inhalation (Spiriva Respimat)
- 1.25mcg/actuation
- 2.5mcg/actuation

**Chronic Obstructive Pulmonary Disease**

Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD); reduction of COPD exacerbations

Spiriva HandiHaler: 2 PO inhalations of 1 capsule (18 mcg) qDay via HandiHaler inhalation device
Spiriva Respimat: 5 mcg (2 actuations; 2.5 mcg/actuation) inhaled PO qDay

**Glycopyrronium**

Seebri Breezhaler (Novartis)

**Adults**

Capsule 50 µg of glycopyrronium

*Chronic Obstructive Pulmonary Disease*

Available as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Once-daily Seebri Breezhaler is approved for use in over 90 countries, including countries within the EU and Latin America, Japan, Canada, Switzerland and Australia.

**Umeclidinium bromide**

Incruse Ellipta (Glaxosmithkline)

**Adults**

Powder for inhalation

- 62.5mcg/actuation

*Chronic Obstructive Pulmonary Disease*

Indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

62.5 mcg (1 actuation) inhaled PO q Day

**Availability of pharmacopoeial standards**

The Pharmacopeia status of the LAMA drugs were verified from the European Pharmacopoeia: https://www.edqm.eu/en/knowledge-database and the entries for tiotropium and glycopyrronium are reproduced here:
### Status
- In use

### Monograph Number
- 02420

### English Name
- Tiotropium bromide monohydrate

### French Name
- Tiotropium (bromure de) monohydraté

### Latin Name
- Tiotropii bromidum monohydricum

### Pinyin Name

### Chinese Name

### Pharmacopea
- 28.2

### Published in English Supplement
- 9.3

### Published in French Supplement
- 9.3

### Chromatogram
- Available

### Additional Information
- Not available

### History
- View history

### Interchangeable (ICH Q4B)
- NO

### Chapter 5.6
- Pharmacopoeial harmonisation

### Reference Standards

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### Practical Information

- **Test(s)**
  - Brand Name/Information
  - Related substances:
    - Zorbax SB-C3
    - Impurities G and H: Merck HPLC 50F254
  - Related substances:
    - DO (dwell volume used for the development of the method) = 0.8 ml.
    - Water: Hydralal Composite S

### CEP

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6. Whether listing is requested as an individual medicine or as a representative of a pharmacological class
The present application requests the inclusion of the LAMA inhaler as representative of a pharmacological class i.e. LAMA.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Document

GOLD document (1) proposes the assessment of COPD based on the patient’s level of symptoms, future risk of exacerbations, the extent of airflow limitation, the spirometric abnormality, and the identification of comorbidities. The “ABCD” assessment tool approaches pharmacologic management according to symptom burden and exacerbation risk. LAMA medication is included in patients in groups B, C and D alone or associated with other drugs. Only less symptomatic and non-exacerbating group A patients can be treated with “any BD”.

8. Information supporting the public health relevance

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death in the world and affects about 10% of the adult global population.

The COPD burden will undoubtedly increase in the coming decades because of continued exposure to risk factors tobacco, outdoor and indoor pollution an aging population and increased childhood survival.

It is well known that there are wide disparities between countries in access to healthcare however, access to spirometry and basic COPD medications show much greater inequalities.

There is a need to raise awareness of COPD to emphasize the importance of accurate diagnosis and ensure drugs with proven efficacy and safety are available.
9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

We searched systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving LAMAs in the Database of Abstracts of Reviews of Effectiveness.

We identified the following studies in DARE:

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<tr>
<th>Year</th>
<th>Database</th>
<th>Title</th>
<th>Summary</th>
<th>Abstract</th>
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<td>2014</td>
<td>DARE</td>
<td>Aclidinium bromide for stable chronic obstructive pulmonary disease</td>
<td>Cochrane Database of Systematic Reviews: Reviews</td>
<td>[Abstract of a Cochrane Review]</td>
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<td>2014</td>
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<td>Aclidinium bromide (Tudorza Genuair - Almirall Canada Ltd.) indication: chronic obstructive pulmonary disease</td>
<td>Canadian Agency for Drugs and Technologies in Health (CADTH)</td>
<td>Authors' conclusions: The Canadian Drug Expert Committee (CDEC) recommends that aclidinium bromide be listed for the treatment of chronic obstructive pulmonary disease (COPD) if the following conditions are met: • List in a manner similar to other long-acting antimuscarinic antagonists (LAMAs). • Drug plan costs for aclidinium bromide should not exceed the cost of any other LAMA.</td>
</tr>
<tr>
<td>2014</td>
<td>NHS EED</td>
<td>Cost-effectiveness of the LABA/LAMA dual bronchodilator indacaterol/glycopyrronium in a Swedish healthcare setting</td>
<td>Respiratory Medicine</td>
<td>Economic evaluation</td>
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<td>2014</td>
<td>DARE</td>
<td>Long-acting beta2-agonists and long-acting muscarinic antagonists in a combined inhaler versus either agent alone or placebo for chronic obstructive pulmonary disease</td>
<td>Cochrane Database of Systematic Reviews: Reviews</td>
<td>[Abstract of a Cochrane Review]</td>
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<td>2014</td>
<td>DARE</td>
<td>Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis</td>
<td>Cochrane Database of Systematic Reviews: Reviews</td>
<td>[Abstract of a Cochrane Review]</td>
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</table>
Additional searches for relevant reviews were undertaken in PubMed which identified relevant papers.

Furthermore, the Cochrane Database of Systematic Reviews was also interrogated for additional evidence, which are summarized here:

- Oba et al (Oba, Keeney et al. 2018)

For this 2018 Cochrane review, Oba collected and analysed data from 99 studies, including a total of 101,311 participants with advanced COPD, using a special method called network meta-analysis, which enabled us to simultaneously compare the four inhaler groups and 28 individual inhalers (4 LABAs, 5 LAMAs, 9 LABA/ICS combinations, and 10 LABA/LAMA combinations). They found that LABA/LAMA combination was the best treatment, followed by LAMA, in preventing flare-ups although there was some uncertainty in the results. Combination inhalers (LABA/LAMA and LABA/ICS), are more effective for controlling symptoms than single-agent therapies (LAMA and LABA), in general. The LABA/LAMA combination was better than LABA/ICS combination, especially in people with a prior episode of flare-ups. The LABA/ICS combination had a higher incidence of severe pneumonia compared to the others. They did not find a difference in benefits and harms, including side effects, among individual inhalers within the same treatment groups.

Conclusions drawn were that the LABA/LAMA combination is likely the best treatment in preventing COPD flare-ups. LAMA-containing inhalers appear to have an advantage over those without LAMA for preventing flare-ups. Combination inhalers (LABA/LAMA and LABA/ICS), appear more effective for controlling symptoms than single-agent therapies (LAMA and LABA). Inhaled steroids carry an increased risk of pneumonia.

Representative LABA examples from Oba et al

Figure 6.1 LAMA vs LABA for moderate to severe exacerbations, favouring LAMAs.
Kew et al (Kew, Dias et al. 2014) conducted a Cochrane network meta-analysis in 2014 to assess the benefits of each type of treatment (e.g. long-acting beta2-agonists) relative to the others for quality of life and lung function. Kew also looked at how much individual treatments varied (e.g. How different were the three inhaled steroids from one other?) and whether particular treatments were more effective than others. Kew assessed the data for six months and 12 months separately and reported six months as the primary findings.

Kew found 71 relevant studies, but not all measured the outcomes we were interested in. Forty-two studies were included in the quality of life analyses (measured on St George's Respiratory Questionnaire), and 46 were included in the lung function analyses. Evidence from good quality and similar trials supported LABA/ICS combinations as the most likely treatment strategy to bring the greatest improvement to quality of life and lung function. Combination therapy gave an average benefit of 3.9 units over placebo at six months. LAMAs and LABAs were ranked second and third at six months (-2.63 and -2.29 units, respectively), especially when unreliable trials were not included, but a large degree of overlap in the estimates was noted. Combination LABA/ICS was the highest ranked class for trough forced expiratory volume in one second (FEV1), with mean improvement over placebo of 133 mL at six months (95% credible Interval (CI) 101 to 164). As was the
case for SGRQ, LAMAs (mean difference (MD) 104, 95% CrI 82 to 125) were ranked just ahead of LABAs (MD 99, 95% CrI 72 to 128) at six months, and ICSs were the lowest ranked class (MD 65, 95% CrI 33 to 97). For both outcomes, the effects of LABA and ICS used alone appeared to increase when used together for six months, but initial differences between the treatment classes were less obvious after a year of treatment.

Kew concluded that quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and 12 months. Overall LAMA and LABA inhalers had similar effects, particularly at 12 months. The network has demonstrated the benefit of ICS when added to LABA for these outcomes in participants who largely had an FEV1 that was less than 50% predicted, but the additional expense of combination inhalers and any potential for increased adverse events (which has been shown by other reviews) require consideration.

- Ni et al (Ni, Soe et al. 2014)

Ni included 12 studies involving 9547 COPD patients in this 2014 Cochrane review treated over a period of four to 52 weeks. These studies were sponsored by drug companies and were well designed. Both patients and the people doing the research did not know which treatment the patients were getting; although in one study one treatment was known to both parties. More men than women took part, and they were mostly Caucasians. They were in their 60s and had smoked a lot in their lives. These people had moderate to severe symptoms when they started treatment. Aclidinium did not reduce the number of people with flare-ups that need additional drugs. There was little or no difference in deaths or serious side effects between aclidinium and a dummy inhaler. Aclidinium inhalers improved quality of life more than the dummy inhalers. People who took aclidinium had fewer hospital admissions due to serious flare-ups. Based on our results, among 1000 COPD patients using a dummy inhaler over four weeks to one year 37 would have severe flare-ups needing hospital admission. Only 17 to 33 patients out of 1000 would require hospital admission if they were using aclidinium inhalers. Ni also set out to compare this new medication with tiotropium, which is already used to treat COPD. There were only two studies for this comparison thus they could not be sure how aclidinium compared to tiotropium. Ni also could not compare aclidinium with another well known inhaler
that contains the drug formoterol because of unreliable data. For the comparison of aclidinium inhalers and dummy inhalers, the Investigators were confident that there are benefits in terms of the number of hospitalisations and patients' quality of life; we are less certain about the numbers of flare-ups needing additional drugs and serious side effects. They did not have enough information to assess any effect on the number of deaths nor enough information to reliably compare aclidinium with tiotropium or formoterol. They concluded that Aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable COPD compared to placebo. Overall, aclidinium did not significantly reduce mortality, serious adverse events or exacerbations requiring oral steroids or antibiotics, or both.

• Ni et al 2018 (Ni, Moe et al. 2018)

In 2018, Ni also published a Cochrane review of studies on aclidinium and formoterol combination and included seven studies involving 5921 people with COPD which ranged from four weeks to one year long. Most participants were men in their 60s, moderate-to-heavy smokers, around half of whom were current smokers. They had moderate-to-severe symptoms of COPD when they started treatment. People in the studies took either combined inhalers containing aclidinium and formoterol or aclidinium or formoterol or placebo through a similar inhaler. People taking combined inhaler and aclidinium inhaler were not different in terms of flare-ups that need additional medicines, quality of life, hospitalisations, side effects or serious side effects. However, they were less breathless than those taking aclidinium inhaler. Fourteen people with COPD would need to be treated with combined inhalers to have one additional person with a clinically significant improvement in breathlessness. People on combined inhalers were likely to have fewer flare-ups, side effects and symptoms and a better quality of life compared to those taking formoterol inhaler. But, there was little or no difference in hospital admissions due to severe flare-ups, serious side effects or the risk of dying. When compared to dummy inhalers, people taking combined inhalers experienced less breathlessness and better quality of life. Seven people with COPD would need to be treated with combined inhaler to achieve a significant improvement in quality of life than dummy inhaler. For flare-ups, hospital
admissions, side effects, serious side effects and death, there was no difference between combined and dummy inhalers. Ni had to interpret the results carefully as all the included studies were sponsored by pharmaceutical companies, which could have led to bias. However, the included studies were generally conducted in a systematic and acceptable manner. The Investigators were confident that combined inhalers are more effective than single or dummy inhalers at improving breathlessness and lung function. However, they were less certain about its effects on flare-ups, hospital admissions, quality of life and side effects.

Conclusions made stated that combined inhalers are more effective than individual or dummy inhalers for relieving breathlessness and improving lung performance. They also lead to better quality of life than formoterol or dummy inhalers. However, they are not different from individual or dummy inhalers in terms of flare-ups or hospital admissions. These combined inhalers have similar safety profiles as individual or dummy inhalers in terms of death, side effects or serious side effects. Combined inhalers probably had lesser side effects and moderate flare-ups than formoterol, but further studies are needed to confidently support this finding. In summary, the combined inhalers are an effective option for treatment of COPD and appear to have a similar safety profile to individual or dummy inhalers.

- Farne et al 015 (Farne and Cates 2015)

In this 2015 Cochrane systematic review, the Investigators found 10 studies involving 10,894 participants comparing the long-term effectiveness and side effects of combining tiotropium with a LABA. The combination of tiotropium plus LABA resulted, on average, in a slightly better quality of life and lung function for the participants compared to using only either tiotropium or a LABA alone, but did not show a difference in hospital admissions or death. The combination treatment also reduced the risk of episodes of acutely worse symptoms ("exacerbations"), compared to a LABA alone but not tiotropium. There were not enough data to determine the risks and benefits of the different types of LABA.

The conclusions were that this review indicated a 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, and this translated into a small increase in the number of responders on combination treatment. In addition, adding tiotropium to
LABA reduced 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. While it is possible that this is affected by higher attrition in the tiotropium group, one would expect that participants withdrawn from the study would have had less favourable outcomes; this means that the expected direction of attrition bias would be to reduce the estimated benefit of the combination treatment. The results were largely from studies of olodaterol and there was insufficient information to assess whether the other LABAs were equivalent to olodaterol or each other.

Lastly, we identified a recent NICE guideline (Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline. Published: 5 December 2018. nice.org.uk/guidance/ng115). The recommendations are reproduced here:

Inhaled combination therapy

Inhaled combination therapy refers to combinations of long-acting muscarinic antagonists (LAMA), long-acting beta2 agonists (LABA) and inhaled corticosteroids (ICS).

The evidence on triple therapy (LAMA+LABA+ICS) is being reviewed as part of the 2019 update to this guideline. This update is expected to publish in June 2019.

1.2.10 Do not assess the effectiveness of bronchodilator therapy using lung function alone. Include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. [2004]

1.2.11 Offer LAMA+LABA[2] to people who:

- have spirometrically confirmed COPD and
- do not have asthmatic features/features suggesting steroid responsiveness and
- remain breathless or have exacerbations despite:
  - having used or been offered treatment for tobacco dependence if they smoke and
  - optimised non-pharmacological management and relevant vaccinations and
  - using a short-acting bronchodilator. [2018]
Summary of comparative effectiveness evidence appraisal

Evidence appraisal for specific long-acting muscarinic antagonists (LAMAs) which result in bronchodilation with a duration of action of 12 to 24 hours, depending on the agent. A number of LAMAs are available, which are delivered via a range of devices; aclidinium, glycopyrronium, tiotropium and umeclidinium (Ellipta).

**Aclidinium:** Aclidinium is a twice daily LAMA. A Cochrane systematic review of 12 RCTs (9,547 participants) showed that, compared to placebo, aclidinium resulted in marginal improvements in quality of life and FEV\textsubscript{1}, and reduced the number of patients with exacerbations requiring hospitalisation (NNT 77, 95% CI 51 to 233) (Ni, Soe et al. 2014) [evidence level I]. Aclidinium has also been shown to reduce the rate of moderate to severe exacerbations (OR 0.80) (Wedzicha, Agusti et al. 2016) [evidence level I].

**Glycopyrronium:** Once daily glycopyrronium demonstrated significant improvement in spirometry and a reduction in the rate of moderate to severe exacerbations, but no difference in quality of life, compared with placebo (D'Urzo, Ferguson et al. 2011, Kerwin, Hebert et al. 2012) [evidence level II]. In an RCT comparing glycopyrronium to tiotropium, there was no difference in FEV\textsubscript{1}, dyspnoea, quality of life, exacerbation rate or adverse effects (Chapman, Beeh et al. 2014) [evidence level II].

**Tiotropium:** Once daily tiotropium resulted in improved quality of life, and reduced exacerbation rates (OR 0.78, 95% CI 0.70 to 0.87; NNT 16, 95% CI 10 to 36) compared to placebo, in a Cochrane systematic review of 22 studies (23,309 participants) (Karner, Chong et al. 2014) [evidence level I]. Tiotropium improved FEV\textsubscript{1} (mean difference 119 mL, 95% CI 113 to 125), and there was no overall difference in mortality. In a 2 year RCT of 841 COPD patients with post-bronchodilator FEV\textsubscript{1} ≥50% predicted, tiotropium resulted in a significantly higher FEV\textsubscript{1} (mean difference of 157 ml, 95% CI 123 to 192) and reduced annual decline in post-bronchodilator FEV\textsubscript{1} (mean difference 22 ml per year, 95% CI 6 to 37), compared to placebo (Zhou, Zhong et al. 2017) [evidence level II]. However, there was a high withdrawal rate and 40% were current smokers.
Compared to ipratropium, tiotropium had beneficial effects for quality of life, dyspnoea and exacerbation rates (Yohannes, Willgoss et al. 2011) [evidence level I]. Compared to LABAs, tiotropium reduced exacerbation rates (Vogelmeier, Hederer et al. 2011, Decramer, Chapman et al. 2013) [evidence level II], whereas effects were heterogeneous for quality of life, compared to various LABAs (Chong, Karner et al. 2012, Decramer, Chapman et al. 2013) [evidence level II]. A Cochrane meta-analysis comparing treatment with tiotropium [HandiHaler or Respimat] with ipratropium bromide (via MDI) for patients with stable COPD found that tiotropium treatment, 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 were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD (Cheyne, Irvin-Sellers et al. 2015).

**Umeclidinium**: Once-daily umeclidinium significantly improved lung function, dyspnoea and quality of life, compared with placebo (Trivedi, Richard et al. 2014) [evidence level II]. Umeclidinium resulted in a greater improvement in FEV\textsubscript{1} than tiotropium, but there were no significant differences between umeclidinium and tiotropium for dyspnoea, SGRQ or CAT scores (Feldman, Maltais et al. 2016) [evidence level II].

**Network meta-analyses of LAMAs**: A network meta-analysis of LAMAs versus placebo showed that there were no statistically significant differences among LAMAs in preventing moderate-to-severe COPD exacerbations (Oba and Lone 2015) [evidence level I]. Tiotropium HandiHaler was the only LAMA formulation which reduced severe exacerbations (HR 0.73; 95% CI 0.60– 0.86). Another network meta-analysis showed that current LAMAs have similar efficacy for change in FEV\textsubscript{1}, SGRQ, dyspnoea and rescue medication use (Ismaila, Huisman et al. 2015) [evidence level I]. However, with few head to head comparisons of LAMAs available, the choice of LAMA and inhaler device depends on patient and clinician preferences.
A meta-analysis of 9 studies of LAMA vs. LABA inhalers (17,120 COPD patients, with tiotropium as the most common LAMA) showed that LAMAs had reduced exacerbation rates (RR 0.88, 95% CI 0.84 to 0.93) and exacerbation-related hospitalisations (RR 0.78, 95% CI 0.69 to 0.87), compared to LABAs (Maia, Pincelli et al. 2017) [evidence level I].

10. Review on harms and toxicity: summary of evidence on safety

Adverse effects
Extensive use of this class of agents in a wide range of doses and clinical settings has shown them to be very safe. Inhaled anticholinergic drugs are poorly absorbed which limits the systemic effects observed with atropine (Tashkin 2010). The main side effect is dryness of mouth (Disse, Speck et al. 1999, Tashkin 2010).

Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship (Kesten, Jara et al. 2006). Some patients using ipratropium report a bitter, metallic taste.

An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported (Michele, Pinheiro et al. 2010). In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk (Tashkin 2010).

Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat® inhaler (Verhamme, Afonso et al. 2013), the findings of a large trial observed no difference in mortality or exacerbation rates when comparing tiotropium in a dry-powder inhaler and the Respimat® inhaler (Wise, Anzueto et al. 2013).

There are less safety data available for the other LAMAs, but the rate of anticholinergic side effects for drugs in this class appears to be low and generally similar
Use of solutions with a facemask can precipitate acute glaucoma, probably as a direct result of the contact between the solution and the eye (Mulpeter, Walsh et al. 1992, Karabis, Lindner et al. 2013).

**Relevant available data on safety:**

Adverse effects of LAMAs notably include dry mouth, constipation and urinary retention (Halpin, Dahl et al. 2015) and as described above.

A safety study showed similar rates of death and exacerbations with tiotropium HandiHaler and tiotropium Respimat (Wise, Anzueto et al. 2013) [evidence level II].

**Summary of regulatory status of the medicine**

LAMA is approved for use in various jurisdictions as follows:

**EMA in the EU:**

- Tiotropium - List of nationally authorised medicinal products. EMA/356882/2017

**Other LAMA medicines in the same class**

- Aclidinium bromide (Bretaris Genuair) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
- Glycopyrronium (Seebri Breezhaler) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
- Umeclidinium bromide (Incruse Ellipta (previously Incruse)) Indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
FDA in USA for Tiotropium:
- SPIRIVA (TIOTROPIUM BROMIDE) | NDA #021395 | POWDER; INHALATION | Prescription | BOEHRINGER INGELHEIM
- SPIRIVA RESPIMAT (TIOTROPIUM BROMIDE) | NDA #021936 | SPRAY, METERED; INHALATION | Prescription | BOEHRINGER INGELHEIM
- SPIRIVA RESPIMAT (TIOTROPIUM BROMIDE) | NDA #207070 | SPRAY; INHALATION | Prescription | BOEHRINGER INGELHEIM

TGA in Australia for Tiotropium:
- ARTG ID 81525 - SPIRIVA is indicated for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease
- (COPD). SPIRIVA is indicated for the prevention of COPD exacerbations.
- ARTG ID 132578 - COPD:
  - SPIRIVA RESPIMAT is indicated for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD). SPIRIVA RESPIMAT is indicated for the prevention of COPD exacerbations.

To our knowledge, generics are not yet available.

11. Available data on cost-effectiveness within the pharmacological class or therapeutic group

The synthesis of the current data is clearly summarised in a systematic literature search of 18 recent pharmacoeconomic analyses of COPD maintenance treatments (van der Schans, Goossens et al. 2017). The Investigators found 6 papers reporting the cost effectiveness of LAMA monotherapy. Many studies were funded by the manufacturer, and all studies indicated favourable cost effectiveness. Exacerbation and mortality rates were found to be the main drivers of cost effectiveness. A Bayesian comparison of Pair-wise Meta Analyses (PMA) and Network Meta Analyses (NMA) of COPD treatments reported that at $40,000/QALY threshold, PMA suggested LAMA had a 30% probability of being the most cost-effective whereas the NMA suggested that LAMA had a 19% probability of being cost-effective (Thorlund, Zafari et al. 2014).

It should be noted that the Investigators considered that the QALYs gained was small and most studies poorly represented the cost effectiveness of real-life medication use (van der Schans, Goossens et al. 2017). Others have noted potential issues with adherence (Punekar, Landis et al. 2015).

**Representative costs in Australia and USA for the examplar medication**

**Australia**
Spiriva 18 mcg Handihaler: registered, May 2002, launched
- Ex-factory Price: 38.43 AUD monthly costs (30day pack).

Spiriva Respimat 2.5 mcg inhalation solution: Registered April 2008. Launched
- Ex-factory Price: 38.43 AUD (monthly costs 30 day pack)

**USA**
Spiriva 18 mcg Handihaler: registered, Jan 2004, launched
  • WAC Price: $429.47 (as of Jan 2019) monthly costs (30day pack).

Spiriva Respimat 2.5 mcg inhalation solution: Registered Sept 2014. Launched
  • WAC Price: $429.47 (as of Jan 2019) monthly costs (30day pack).
References


