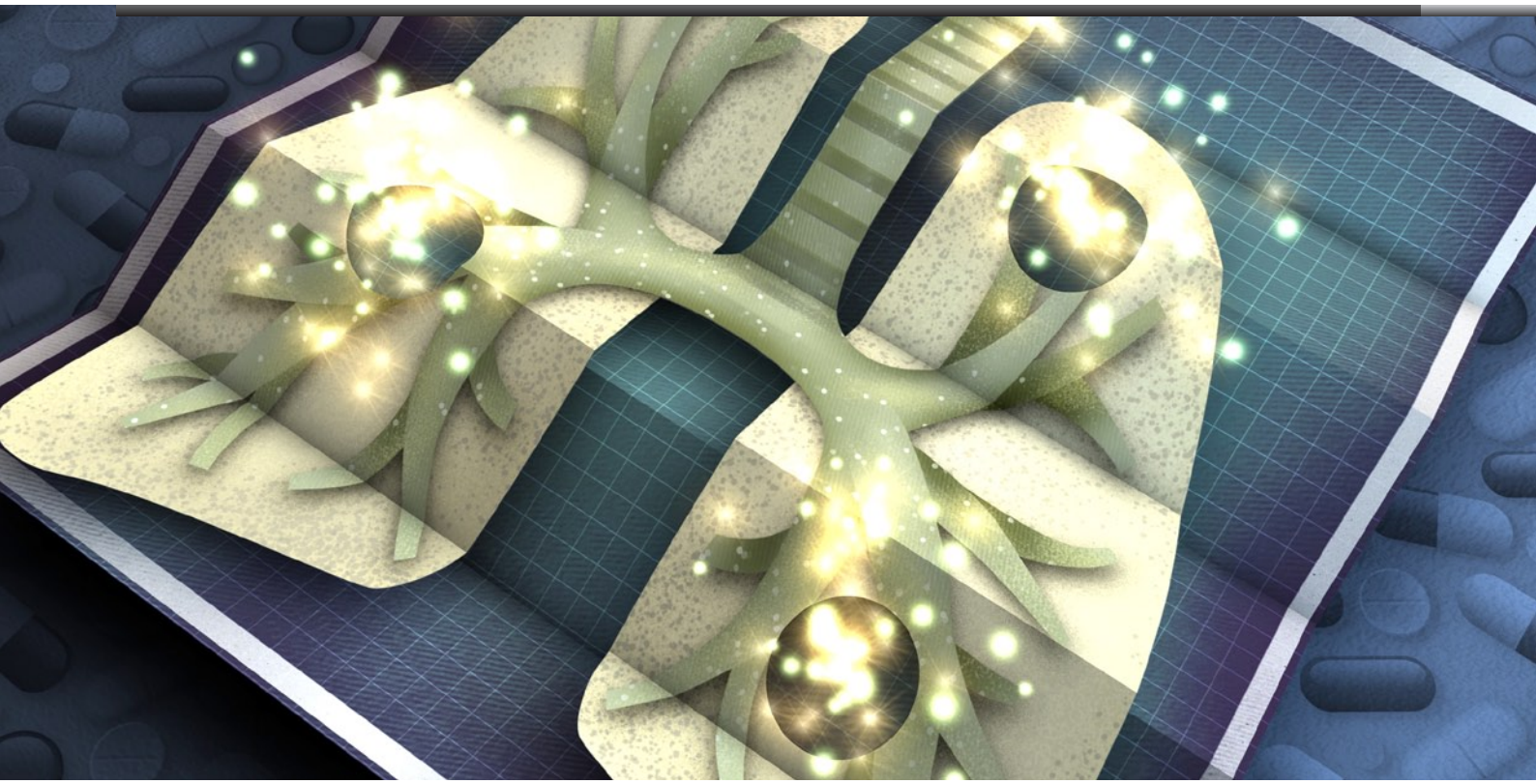

Newly-subsidised medicines for the treatment of patients with COPD

Subsidy changes for medicines used to treat patients with COPD came into effect on March 1, 2016. In this article we discuss how these changes affect the management of patients with COPD and introduce prescribers to medicines new to the New Zealand market, highlight inhaled combination medicines and an inhaler device that were not previously available and provide updates on access and subsidies.

KEY PRACTICE POINTS

- Umeclidinium (Incruse*) and glycopyrronium (Seebri) may become the most common LAMAs** for patients with COPD who are not already receiving treatment with a LAMA as they do not require Special Authority approval
- Three combination LAMA/LABA inhalers, olodaterol + tiotropium (Spiolto), umeclidinium + vilanterol (Anoro) and glycopyrronium + indacaterol (Ultibro) are now available; combination LAMA/LABAs were not previously subsidised in New Zealand
- The choice of inhaled LAMAs and combination LABA/LAMAs is largely based on the ability of patients to use the various devices and patient and clinician preference; there is no robust evidence that one of these medicines has greater clinical efficacy than any other
- A new ICS/LABA, fluticasone + vilanterol (Breo) that only requires once-daily dosing is now available for patients with COPD; previous subsidised options required twice daily dosing, i.e. fluticasone + salmeterol (Seretide, Rexair) and budesonide + formoterol (Symbicort, Vannair)

* Generally, bpac^{nz} does not use trade names where referring to medicines. An exception has been made in this article, as there is the potential for prescriber confusion. The trade names of the various inhaler devices are included in Table 2.

** Abbreviations used for inhaled medicines: LAMA = Long-acting muscarinic receptor antagonist, LABA = Long-acting beta$_2$ agonist, DPI = Dry powder inhaler, MDI = metered dose inhaler, ICS = Inhaled corticosteroid, SABA = Short-acting beta$_2$ agonist, SAMA = Short-acting muscarinic receptor antagonist.

Treatment options for patients with COPD have increased

The range of subsidised medicines used to treat patients with COPD in New Zealand has been transformed over the past 18 months. In November, 2014, glycopyrronium (Seebri DPI), a LAMA, and indacaterol (Onbrez DPI), a LABA, were added to the pharmaceutical schedule. On 1 March, 2016, the number of subsidised medicines available to patients in New Zealand with COPD was further increased:

- Two new medicines may now be prescribed that were not previously available:

- **Umeclidinium** (Incruse DPI), a LAMA, is a new medicine to New Zealand and is subsidised in single medicine and combination inhalers
- **Olodaterol**, a LABA, is a new medicine to New Zealand and is subsidised as a combination inhaler

- Three combination LAMA/LABAs inhalers, **glycopyrronium + indacaterol** (Ultibro DPI), **olodaterol + tiotropium**, (Spiolto MDI) and **umeclidinium + vilanterol** (Anoro DPI) are now subsidised. Combination LAMA/LABA inhalers were not previously subsidised in New Zealand.
- A new combination inhaled corticosteroid (ICS)/LABA, **fluticasone + vilanterol** (Breo DPI) t**hat only requires once-daily dosing** is now available for patients with COPD. Previously subsidised ICS/LABA inhalers required twice daily dosing, i.e. fluticasone + salmeterol (Seretide, Rexair MDIs) and budesonide + formoterol (Symbicort DPI, Vannair MDI). Vilanterol has only recently become available in New Zealand and is also available as a LAMA/LABA in combination with umeclidinium.
- The Special Authority approval criteria has been removed from the LAMA inhaler glycopyrronium (Seebri DPI) and the combination ICS/LABA budesonide + formoterol (Symbicort DPI, Vannair MDI)
- A new type of tiotropium inhaler (Spiriva MDI) is also now available

Umeclidinium: a new LAMA not previously available

Umeclidinium (Incruse DPI) is a LAMA that is new to the New Zealand market. As of March 1, 2016 umeclidinium is available without restriction for patients with COPD, provided the prescription is endorsed* by the prescriber that the patient has been diagnosed with COPD by spirometry.

The pharmacology of umeclidinium

Umeclidinium, like tiotropium, preferentially binds to M_3 acetylcholine muscarinic receptors to induce bronchodilation.[1] The medicine has an effect within 5 to 15 minutes of inhalation, peak efficacy is at three hours and therapeutic levels last for more than 24 hours.[1] Patients achieve a steady-state concentration of umeclidinium after 14 days of dosing.[1]

Umeclidinium is reported to have been used in multiple clinical trials with similar frequencies of adverse effects as placebo and tiotropium.[1] Umeclidinium should be used cautiously with patients who have urinary retention or narrow-angle glaucoma due to its antimuscarinic activity.[1]

Combination LAMA/LABA inhalers are now available in New Zealand

Three LAMA/LABA combination inhalers are now subsidised with Special Authority approval for patients with COPD with the diagnosis confirmed by spirometry (See: "The importance of spirometry in COPD diagnosis"):

- Glycopyrronium + indacaterol (Ultibro Breezhaler)
- Tiotropium + olodaterol (Spiolto Respimat)
- Umeclidinium + vilanterol (Anoro Ellipta)

Glycopyrronium (Seebri DPI – a LAMA) and **indacaterol** (Ombrez DPI – a LABA) have been subsidised in New Zealand since November, 2014 as single medicine inhalers.

For further information see: "Medicine updates", BPJ 65 (Dec, 2014).

The pharmacology of olodaterol

Olodaterol, a LABA, is new to the New Zealand market and is only available in combination with tiotropium.

Olodaterol was specifically designed for use in combination with tiotropium.[2] Peak plasma concentration occurs 10–20 minutes after inhaling the medicine and patients experience bronchodilation lasting at least 24 hours.[3]

Olodaterol is associated with similar adverse effects to other LABAs, including increased heart rate, raised blood pressure and hypokalaemia. Caution is required if olodaterol is prescribed to patients with cardiovascular disorders, QT prolongation, thyrotoxicosis or convulsive disorders.[4]

The pharmacology of vilanterol

Vilanterol, a LABA, is relatively new to the New Zealand market and was previously available only in combination with fluticasone as an ICS/LABA inhaler (Breo DPI). Vilanterol is now available in combination with umeclidinium.

Vilanterol has greater selectivity for beta2-adrenergic receptors than formoterol and indacaterol.[5] The onset of vilanterol occurs within five minutes of inhalation and it is effective when taken once daily, due to its long-lasting action.[5]

Vilanterol is associated with similar adverse effects as other LABAs. In a short study in patients with moderate-to-severe COPD there were no changes in blood pressure, ECG, blood glucose or potassium levels in patients taking vilanterol.[5]

* Prescription endorsements should be handwritten or computer-generated by the prescriber and include "certified condition" on the prescription or a statement confirming that the patient has been diagnosed with COPD by spirometry.

How will the changes in medicine subsidy affect the management of patients with COPD?

Smoking cessation, physical activity (including pulmonary rehabilitation) and maintenance of normal body weight remain essential aspects in the management of patients with COPD.

Medicines are prescribed to help patients manage symptoms and reduce their risk of exacerbations. Treatments are introduced in a stepwise manner depending on the severity of the patient's symptoms, the results of spirometry and the patient's quality of life (Table 1).

Step 1: For all patients with symptomatic COPD Short-acting bronchodilators, i.e. inhaled SABAs and SAMAs, are appropriate for patients with mild COPD for use during periods of acute breathlessness.[6, 7] The medicine subsidy changes do not affect the availability of treatment options for these patients:[6, 7]

- Inhaled SABAs, i.e. salbutamol (Respigen, Salair, Salamol, Ventolin MDIs) or terbutaline (Bricanyl DPI)
- An inhaled SAMA, i.e. ipratropium (Atrovent MDI]); or
- An inhaled combination SABA/SAMA, i.e. ipratropium + salbutamol (Duolin HFA MDI)

Table 1: The assessment of COPD severity and the stepwise escalation of pharmacological treatment, adapted from Abramson *et al*, 2014.[6]

Severity	Mild	Moderate	Severe
	■ Few symptoms ■ Breathless on moderate exertion ■ Recurrent chest infections ■ Little or no effect on daily activities ■ FEV_1 = 60 – 80% of predicted	■ Increasing dyspnoea ■ Breathless walking on level ground ■ Increasing limitation of daily activities ■ Cough and sputum production ■ Infections requiring corticosteroids ■ FEV_1 = 40–59% of predicted	■ Dyspnoea on minimal exertion ■ Daily activities severely restricted ■ Experiencing regular sputum production ■ Chronic cough ■ FEV_1 < 40% of predicted
Medicines management	**Check technique of device use and adherence at each visit** – up to 90% of patients do not use devices correctly		
Step 1	**For all patients with COPD** for use during periods of acute breathlessness prescribe an: ■ Inhaled SABA, i.e. salbutamol (Respigen, Salair, Salamol, Ventolin MDIs), terbutaline (Bricanyl DPI) ■ Inhaled SAMA, i.e. ipratropium (Atrovent); or ■ A combination SABA/SAMA, i.e. ipratropium + salbutamol (Duolin HFA MDI)		
Step 2	**For patients with COPD and persistent troublesome dyspnoea** who do not have adequate symptom control while using a short-acting bronchodilator, consider prescribing: ■ A LABA, i.e. salmeterol (Meterol MDI, Serevent MDI and DPI), indacaterol (Onbrez DPI), formoterol◐ (Foradil, Oxis DPIs) ■ A LAMA, i.e. glycopyrronium2 (Seebri DPI), umeclidinium● (Incruse DPI), tiotropium● (Spiriva DPI and MDI)		
Step 2.5	**For patients who are unable to achieve symptom control with a single long-acting bronchodilator** consider a newly-subsidised combination LABA/LAMA inhaler: ■ Glycopyrronium + indacaterol● (Ultibro DPI) ■ Olodaterol + tiotropium● (Spiolto MDI) ■ Umeclidinium + vilanterol● (Anoro DPI)		
Step 3	**For patients with an FEV_1 < 50% of predicted and two or more exacerbations in a 12-month period:** Consider prescribing a fixed-dose combination ICS/LABA: ■ Fluticasone + vilanterol (Breo DPI), once daily ■ Budesonide + formoterol (Symbicort DPI, Vannair MDI), twice daily ■ Fluticasone + salmeterol (Seretide, Rexair MDIs), twice daily		

◐ Partially subsidised without restriction ● Prescription endorsement required for full subsidy ● Special Authority approval required for full subsidy

Step 2: For patients with COPD and persistent troublesome dyspnoea

Long-acting bronchodilators, i.e. inhaled LABAs and LAMAs, are appropriate for patients with persistent and troublesome dyspnoea who do not receive adequate symptom control while using a short-acting bronchodilator.[6]

The medicine subsidy changes have made treatment with inhaled LAMAs and inhaled combination LABA/LAMAs more accessible to patients with COPD. There is no robust evidence that one inhaled LAMA or inhaled combination LABA/LAMA has greater clinical efficacy than any other; treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Subsidised treatment options for LAMAs are:

- **Glycopyrronium** (Seebri DPI) prescribed as one inhalation, once daily, of 50 micrograms of glycopyrronium
- **Umeclidinium** (Incruse DPI) prescribed as one inhalation, once daily, of 62.5 micrograms of umeclidinium bromide
- **Tiotropium** (Spiriva DPI and MDI mist-inhaler) prescribed as either 18 micrograms, once daily (Spiriva Handihaler) or 5 micrograms, once daily (Spiriva Respimat); both provide patients with similar levels of systemic exposure to tiotropium[9]

Subsidised inhaled LABA treatment options remain salmeterol (Meterol MDI, Serevent MDI and DPI), indacaterol (Onbrez DPI) or formoterol (Foradil, Oxis DPIs – partially subsidised).

Umeclidinium and glycopyrronium may become the most common LAMAs

Due to the subsidy change, rather than any evidence of clinical benefit, umeclidinium (Incruse DPI) or glycopyrronium (Seebri DPI) may become the most common LAMAs for patients with COPD who are not already taking a LAMA as they do not require Special Authority approval. Both of these LAMAs are now available without restriction provided the prescription is endorsed by the prescriber that the patient has been diagnosed with COPD by spirometry. Special Authority approval is still required for subsidised treatment with tiotropium. Patients in New Zealand can only receive subsidised treatment with one LAMA at any one time.

Previously, patients with COPD needed to meet Special Authority approval criteria to receive treatment with a LAMA. It is estimated that 1200 people in New Zealand with COPD, who were previously unable to access subsidised LAMA treatment, will benefit from access to umeclidinium or glycopyrronium.[8]

Tiotropium continues to be subsidised under Special Authority approval for patients with COPD who have an FEV_1 < 60% of predicted on spirometry. However, the Special Authority renewal for tiotropium no longer includes the requirement for recent spirometry. General practitioners applying for subsidy renewal for tiotropium must only be satisfied that the patient is adherent with treatment and that their symptoms have improved with treatment.

There is no clear evidence to help decide the preferred LAMA for treatment initiation in patients with COPD; head-to-head trials for these medicines are lacking. For patients with COPD and an FEV_1 < 60%, who have not been previously prescribed a LAMA, i.e. those eligible for treatment with any of the three LAMAs, treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Step 2.5: Combination LABA/LAMAs are now available

An inhaled combination LABA/LAMA is appropriate for patients with COPD who are unable to achieve symptom control with a single long-acting bronchodilator. Three combination LABA/LAMAs that were not previously subsidised in New Zealand are now subject to Special Authority approval (Table 2):

- **Glycopyrronium + indacaterol** (Ultibro DPI) prescribed as 110 + 50 micrograms, once daily
- **Olodaterol + tiotropium** (Spiolto MDI) prescribed as 2.5 + 2.5 micrograms, once daily
- **Umeclidinium + vilanterol** (Anoro DPI) prescribed as 62.5 + 25 micrograms, once daily

The addition of a combination LAMA/LABA inhaler has been reported by a number of studies to improve lung function on spirometry in patients with COPD who are not adequately controlled with a single bronchodilator.[7] The use of combination LAMA/LABAs is thought to decrease the risk of adverse effects compared with increasing the dose of a single bronchodilator.[7]

There is no clear evidence to help decide the preferred combination LABA/LAMA for treatment initiation in patients with COPD; head-to-head trials for these medicines are lacking. Treatment decisions may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Step 3: For patients with an FEV_1 < 50% of predicted and two or more exacerbations in a 12-month period

Fixed-dose inhaled ICS/LABA combinations are appropriate for patients with an FEV_1 < 50% of predicted and two or more exacerbations in 12-month period.[6] Subsidised combination ICS/LABAs for these patients include:[11]

- **Fluticasone + vilanterol** (Breo DPI) a new ICS/LABA inhaler requiring once daily dosing is subsidised without restriction and is prescribed as: one inhalation, once daily, of fluticasone + vilanterol (100 + 25 micrograms)
- **Budesonide + formoterol** (Symbicort DPI, Vannair MDI)

no longer has Special Authority approval criteria* for the treatment of COPD and is available without restriction
The DPI is more appropriate for the treatment of patients with COPD and is prescribed as:
  - Two inhalations, twice daily, of budesonide + formoterol (200 + 6 micrograms); maximum of four inhalations daily
  - One inhalation, twice daily, of budesonide + formoterol (400 + 12 micrograms); maximum of two inhalations daily
- **Fluticasone + salmeterol** (Seretide MDI and DPI, Rexair MDI), twice daily, continues to be subsidised without restriction for patients with COPD (Table 2)

* Prior to March 1, 2016, to receive subsidised treatment with budesonide + formoterol, patients needed to be aged over 12 years and to have been treated with an ICS of at least 800 micrograms per day beclomethasone or budesonide, or 500 micrograms per day fluticasone, and assessed as likely to gain additional benefit from a combination product.

Which combination ICS/LABA inhalers are most effective?

There is no clear evidence to help decide the preferred ICS/LABA combination for patients with COPD; head-to-head trials of these medicines are lacking. The decision of which ICS/LABA is most appropriate for patients who have not been previously treated with an ICS/LABA may be guided by the patient's ability to operate the various devices and patient and clinician preference.

Consider the increased risk of pneumonia before initiating ICS treatment in patients with COPD. The annual risk of pneumonia associated with vilanterol alone in patients with COPD was 3%, compared with 6–7% in patients taking fluticasone + vilanterol.[12]

For further information see: "The optimal management of patients with COPD – Part 1: The diagnosis" and "The optimal management of patients with COPD – Part 2: Stepwise escalation of treatment", BPJ 66 (Feb, 2015).

For further information see: "Are blood eosinophil counts helpful in predicting patient responses to inhaled corticosteroids in COPD?", Page 3.

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The importance of spirometry in COPD diagnosis

COPD cannot be confidently diagnosed in a patient by the presence of symptoms alone; spirometry is required to confirm a diagnosis.[7] Patients in New Zealand with COPD may need to be assessed with spirometry before they are eligible for subsidised treatment with some of the inhaled medicines (Table 2). The peak expiratory flow rate (PEFR) should not be used to diagnose COPD as this is a measure of airflow in the patient's large airways and does not access airflow in the bronchioles.

Spirometry can be reliably performed in primary care, although training in technique and equipment maintenance is required. When performing spirometry a FEV_1/FVC ratio < 0.7 indicates an airflow limitation consistent with COPD.[7] The results of spirometry are used to assess the severity of COPD, in combination with the clinical symptoms and signs of hypoxaemia, hypercapnia, pulmonary hypertension, heart failure and polycythaemia.[6] Spirometry is not recommended to "screen" patients without significant symptoms;[7] testing should be reserved for patients suspected of having COPD.

Table 2: Inhaled medicines subsidised in New Zealand for the treatment of patients with COPD from March 1, 2016 (newly-subsidised medicines are high-lighted ●).[11]

Medicine	Dose and frequency	Inhaler device (trade name)	Subsidy status
Short acting beta$_2$-agonists (SABA)			
Salbutamol	100 – 200 micrograms (one to two inhalations of 100 micrograms), as needed, up to four times daily	Metered dose inhaler (MDI) with use of a spacer recommended (Respigen, Salair, Salamol, Ventolin)	Fully subsidised without restriction and available on Practitioner Supply Order (PSO)
Terbutaline	250 – 500 micrograms (one to two inhalations of 250 micrograms), as needed Maximum single dose: six inhalations Maximum daily dose: 24 inhalations	Breath-activated dry powder inhaler (DPI) loaded when base of device is turned (Bricanyl Turbuhaler)	Fully subsidised without restriction
Long-acting beta$_2$-agonists (LABA)			
Salmeterol	50 micrograms (two inhalations of 25 micrograms), twice daily	MDI (Meterol, Serevent) and breath-activated DPI (Serevent Accuhaler) with each dose contained in a disc of eight doses	Fully subsidised without restriction
Indacaterol	150 – 300 micrograms (one capsule of 150 micrograms or one capsule of 300 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Onbrez Breezhaler)	Fully subsidised without restriction
Formoterol (Eformoterol)	12 micrograms (two inhalations of 6 micrograms, or one capsule of 12 micrograms), once or twice daily	Breath-activated DPI loaded when base of device is turned (Oxis Turbuhaler) and breath-activated device with each dose contained in a capsule (Foradil)	Partially subsidised without restriction
Anticholinergics (SAMA or LAMA)			
Ipratropium (short-acting)	40 micrograms (two puffs of 20 micrograms), four times daily Maximum single dose: 80 micrograms. Maximum daily dose: 240 micrograms	MDI with use of a spacer recommended (Atrovent)	Fully subsidised without restriction
Glycopyrronium (long-acting)	50 micrograms (one inhalation of 50 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Seebri Breezhaler)	Both fully subsidised with an endorsement on the prescription that the patient has been diagnosed with COPD with spirometry. These medicines will not be subsidised if the patient is already taking another subsidised LAMA.
● **Umeclidinium** (long-acting)	62.5 micrograms (one inhalation of 62.5 micrograms), once daily	Breath-activated DPI automatically loaded when opened (Incruse Ellipta)	
Tiotropium (long-acting)	18 micrograms (one capsule of 18 micrograms), once daily	Breath-activated DPI with each dose contained in a capsule (Spiriva HandiHaler)	New prescriptions are fully subsidised with Special Authority for patients with all of the following: ■ Have trialled a short-acting bronchodilator of at least 40 micrograms ipratropium, four times daily for one month ■ Have grade 4 or 5 breathlessness ■ Recent FEV_1 below 60% of predicted ■ Have been offered smoking cessation counselling if currently smoking ■ Have been offered influenza immunisation
	● 5 micrograms (two inhalations of 2.5 micrograms), once daily	MDI containing a solution delivered as mist that does not include propellants (Spiriva Respimat)	

Continued on next page

Medicine	Dose and frequency	Inhaler device (trade name)	Subsidy status
			Tiotropium continued from previous page This medicine will not be subsidised if the patient is already taking another subsidised LAMA. Prescription renewals require that the patient be adherent with treatment and to have experienced an improvement in COPD symptoms.
Combination bronchodilators			
Ipratropium + salbutamol (SABA/SAMA)	20 + 100 micrograms, two puffs, four times daily	MDI with use of a spacer recommended (Duolin HFA)	Fully subsidised without restriction
● **Olodaterol + tiotropium** (LABA/LAMA)	2.5 + 2.5 micrograms, two puffs, once daily	MDI containing a solution delivered as a mist (Spiolto Respimat)	Fully subsidised with Special Authority for patients previously treated with a LAMA who are likely to gain additional benefit from a combination LAMA/LABA. Special Authority renewal requires that patient is adherent and has improved COPD symptom control.
● **Umeclidinium + vilanterol** (LAMA/LABA)	62.5 + 25 micrograms, one puff, once daily	Breath-activated DPI automatically loaded when opened (Anoro Ellipta)	
● **Glycopyrronium + indacaterol** (LAMA/LABA)	110 + 50 micrograms, one puff, once daily	Breath-activated DPI with each dose contained in a capsule (Ultibro Breezhaler)	
Combination ICS/bronchodilators			
● **Fluticasone furoate + vilanterol** (ICS/LABA) Note: the 200 + 25 micrograms inhaler is not indicated for COPD	100* + 25 micrograms, one puff, once daily	Breath-activated DPI automatically loaded when opened (Breo Ellipta)	Fully subsidised without restriction
Budesonide + formoterol (Eformoterol) (ICS/LABA) Note: budesonide + formoterol (100 + 6 micrograms) is used for the treatment of asthma, not COPD	200 + 6 micrograms; two inhalations, twice daily	Breath-activated DPI loaded when base of inhaler is turned (Symbicort Turbuhaler) and MDI with use of a spacer recommended (Vannair)	Fully subsidised without restriction
	400 + 12 micrograms; one inhalation, twice daily	Breath-activated DPI loaded when base of inhaler is turned (Symbicort® Turbuhaler®)	
Fluticasone + salmeterol (ICS/LABA) Note: the 100 + 50 micrograms DPI inhaler is not indicated for COPD	125 + 25 micrograms; two inhalations, twice daily 250 + 25 micrograms; up to two inhalations, twice daily, if symptoms not controlled with 125 + 25 micrograms	MDI with use of a spacer recommended (Seretide, Rexair)	Fully subsidised without restriction
	250 + 50 micrograms; one inhalation, twice daily	Breath-activated DPI with each dose contained in a disc of eight doses (Seretide Accuhaler) Note: MDI 250 + 50 micrograms is not subsidised	

* Important: One inhalation of fluticasone furoate 100 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily.