Indacaterol with glycopyrronium (Ultibro Breezhaler) for chronic obstructive pulmonary disease (IN-da-CAT-er-ol with GLY-co-pi-RO-ni-um)

KEY POINTS

Once-daily maintenance bronchodilator for people with moderate to severe COPD
Indacaterol 110 micrograms / glycopyrronium 50 micrograms (Ultibro Breezhaler 110/50) is a fixed-dose combination of medicines. It provides maintenance bronchodilation for 24 hours after a once-daily dose in people with COPD.

Not PBS listed for first-line bronchodilation therapy in COPD
Patients must have been stabilised on a combination of a long-acting muscarinic receptor antagonist/anticholinergic (tiotropium, glycopyrronium, aclidinium or umeclidinium) and long-acting beta-2 receptor agonist (indacaterol, salmeterol or eformoterol).

Not for use in asthma or mixed airways disease

Similar efficacy and safety to that of both ingredients delivered concurrently
Over 4 weeks, improvements in lung function, symptom reduction, use of rescue medication and rate of adverse events for indacaterol/glycopyrronium 110/50 micrograms FDC were comparable to those for both ingredients inhaled concurrently as single-agent formulations.

PBS listing

Authority required (Streamlined)
Indacaterol/glycopyrronium FDC (Ultibro Breezhaler 110/50) delivered via the single inhaler device is PBS listed as Authority Required (Streamlined) for chronic obstructive pulmonary disease (COPD).

Patients must have been previously stabilised on a combination of a long-acting beta-2 agonist and long-acting muscarinic receptor antagonist taken with separate inhalers.

May be prescribed by nurse practitioners
Indacaterol/glycopyrronium FDC may be prescribed by nurse practitioners as continuing therapy only, when the treatment and prescribing of medicine for a patient has been initiated by a medical practitioner. See the PBS website for more information on nurse practitioner PBS prescribing.

What is it?
Indacaterol/glycopyrronium 110/50 micrograms FDC (Ultibro Breezhaler 110/50) is an inhaled powder containing two bronchodilators with different modes of action: 1

- indacaterol, a long-acting beta-2 agonist producing bronchodilation by stimulation of intracellular adenyl cyclase
- glycopyrronium, a long-acting muscarinic antagonist/anticholinergic that provides bronchodilation by blocking the action of acetylcholine on the muscarinic receptors of airway smooth muscle cells.

Both bronchodilators are long acting, with an onset of action within 5 minutes after inhalation and a duration of effect that is sustained over 24 hours. 1

Indacaterol/glycopyrronium FDC capsules are for inhalation only and are supplied with an inhalation device. 1
EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS COMBINATION DRUG?
Indacaterol/glycopyrronium 110/50 FDC consists of a long-acting beta-2 agonist (LABA) and a long-acting muscarinic antagonist/anticholinergic (LAMA) in a single capsule taken via an inhaler device.

It is used as maintenance treatment for symptom control in patients with moderate to severe COPD who have previously been stabilised on both a LABA and a LAMA in separate inhalers.

It has a similar safety and tolerability profile to that of the components (indacaterol 150 micrograms and glycopyrronium 50 micrograms) delivered concurrently or as monotherapy.

AREAS OF UNCERTAINTY
The long-term clinical effects of indacaterol/glycopyrronium FDC are unknown, as there are no safety data beyond 64 weeks.

Comparative data are available on clinical efficacy and safety of indacaterol/glycopyrronium FDC compared with that of indacaterol or glycopyrronium delivered separately as monotherapy for up to 26 weeks and 64 weeks, respectively.

The comparison between indacaterol/glycopyrronium FDC and the component ingredients delivered concurrently was only a 4-week trial.

WHAT DOES NPS SAY?
COPD stepwise management is complicated and requires patients to discontinue some previous medicines before undertaking new treatment. The In Brief article in this issue of NPS RADAR ‘Pharmacological therapies for COPD in Australia’ provides a list of currently available medicines and explains which medicines may be used in combination.

Indacaterol/glycopyrronium FDC is PBS listed for use in people with moderate to severe COPD who have been stabilised on combination therapy of a LABA and a LAMA taken with separate inhalers.

It should not be used concurrently with any other product containing a short-acting or long-acting muscarinic antagonist (SAMA or LAMA) or long-acting beta-2 agonist (LABA, or LABA with inhaled corticosteroid [LABA/ICS]). A short-acting beta-2 agonist (SABA) should be used for symptom relief as needed while taking this combination FDC.

Indacaterol/glycopyrronium FDC is as effective and safe as concurrent delivery of indacaterol 150 micrograms and glycopyrronium 50 micrograms in separate inhalers, and more effective at improving lung function than either ingredient delivered alone.

Long-acting bronchodilators are the mainstay of pharmacological management of COPD. When symptoms persist or are not controlled on a single long-acting bronchodilator, consult guidelines before considering stepping up to a combination product and to inform a choice of products suitable for combination use.

Consider that bronchodilators delivered in a fixed-dose combination may simplify treatment and may be preferred by patients.

ADDITIONAL INFORMATION
See the online version of this article at www.npsradar.org.au/indacaterol-glycopyrronium for an assessment of the evidence quality for indacaterol/glycopyrronium using the ‘GRADE’ criteria.
Who is it for?

Use indacaterol/glycopyrronium FDC for maintenance bronchodilation treatment in patients with moderate to severe COPD.¹

Do not use as first-line bronchodilation therapy in COPD

For PBS-listed use, patients must have been stabilised on a combination of a LAMA (tiotropium, glycopyrronium, aclidinium or umeclidinium) and a LABA (indacaterol, salmeterol or eformoterol), in separate devices.

Not for asthma, mixed airways disease or acute episodes of bronchospasm

Indacaterol/glycopyrronium FDC is not for people with asthma, as there are insufficient data to support its use for this indication.

Excluding a diagnosis of asthma or mixed airways disease before starting indacaterol/glycopyrronium FDC.

Do not use as rescue therapy for treatment of acute episodes of bronchospasm.¹

Not for people under 18 years of age

COPD affects adults only, and indacaterol/glycopyrronium FDC is not for use in patients aged under 18 years.¹

Where does it fit?

Inhaled bronchodilators are first-line therapy for pharmacological management of COPD.² ³

Indacaterol/glycopyrronium FDC is a once-daily LABA/LAMA combination bronchodilator that provides a single-inhaler alternative to a LABA and LAMA in two separate inhaler devices.

Combination products such as indacaterol/glycopyrronium FDC can simplify treatment regimens in COPD when used in line with a stepwise approach to management.⁴

Use for maintenance treatment in moderate to severe COPD

Current recommendations for stepwise management support using a LABA and a LAMA for symptom control in patients with moderate (40–59% FEV₁, predicted) or severe (< 40% FEV₁, predicted) COPD.⁵

Indacaterol/glycopyrronium FDC is an option for patients who have been previously stabilised on a combination of a LABA and LAMA taken in two separate inhalers.¹

Indacaterol/glycopyrronium FDC can only be used with a SABA

It should not be used concomitantly with any other inhaler containing a short-acting or long-acting muscarinic antagonist (SAMA or LAMA) or long acting beta-2 agonist (LABA or LABA/ICS). It may be used with a short-acting beta-2 agonist as needed for symptom relief (SABA).² ³ ⁵

Medicines that are replaced by this FDC should be returned to a pharmacy for safe destruction.

How does it compare?

Combination therapy involving the bronchodilator action of a LABA and a LAMA for moderate to severe COPD has been shown to be more effective than single bronchodilator monotherapy (either a LABA or LAMA in a single inhaler) due to the complementary mechanism of action of the individual components.⁶-⁹

To date, all trials assessing efficacy for indacaterol/glycopyrronium FDC have recruited people aged over 40 with moderate or severe COPD who were current or ex-smokers with a smoking history of at least 10 pack-years.¹ ² ⁷-¹¹

People with recent acute exacerbations of their COPD were mostly excluded from trials, and those taking an ICS at baseline continued use of the ICS for the duration of the trial.² ³ ¹¹

Comparable efficacy to that of both drugs delivered concurrently

In the 4-week BEACON trial of people with moderate to severe COPD (n = 193), indacaterol/glycopyrronium 110/50 micrograms FDC delivered via a single inhaler (Breezhaler) improved lung function to a degree comparable with concurrent indacaterol 150 micrograms and glycopyrronium 50 micrograms delivered via separate inhalers (both Breezhalers).
Lung function was primarily determined by trough FEV₁ at 4 weeks and did not differ between the two groups. Other measures of lung function such as FEV₁ \( \text{AUC}_{0-4} \) were also similar between groups at day 1 and week 4.¹

A similar reduction in self-reported symptoms (eg, coughing, wheezing, sputum production, breathlessness) and use of rescue medicine was seen between the two groups. Exacerbations and quality of life measures were not reported.¹¹

**Greater efficacy than for monotherapy with either drug**

Compared with monotherapy with either indacaterol 150 micrograms or glycopyrronium 50 micrograms taken for 26 weeks in the SHINE trial (n = 2144), people taking indacaterol 110 micrograms / glycopyrronium 50 micrograms FDC showed significantly greater improvements in lung function throughout the trial period.

The primary endpoint at 26 weeks, trough FEV₁, was 70 mL and 90 mL higher (p < 0.001), than for indacaterol and glycopyrronium, respectively taken as monotherapy.⁷

The clinical relevance of such differences is unclear given most trials consider an improvement of ≥100 mL to be a clinically relevant change in lung function in COPD.¹²

FEV₁ \( \text{AUC}_{0-4} \). Peak FEV₁ and FEV₁ \( \text{AUC}_{0-24} \) were all significantly improved over the trial period in patients taking indacaterol/glycopyrronium FDC compared with those taking indacaterol or glycopyrronium alone.⁷

People assigned to the FDC did not report a reduction in breathlessness, as measured by improvement in total dyspnoea index focal scores,⁶ or improvement in health status, as measured by St George’s respiratory questionnaire (SGRQ), which were secondary outcomes, compared with those taking indacaterol or glycopyrronium alone.⁷

Use of rescue medication was significantly lower for people taking indacaterol/glycopyrronium FDC compared with those taking indacaterol (p < 0.05) or glycopyrronium (p < 0.001) alone.⁷

People who had experienced a recent exacerbation requiring antibiotics, systemic steroids (oral or intravenous) or hospitalisation, within 6 weeks of enrolment, were excluded from the trial. The authors noted that this study did not provide useful information on the effect of indacaterol/glycopyrronium FDC on exacerbations.⁷

In the SPARK trial (n = 2224) comparing indacaterol/glycopyrronium FDC with glycopyrronium alone, people taking the FDC experienced greater improvements in lung function at 64 weeks.

Trough FEV₁ was significantly higher (70–80 mL difference, p < 0.0001) in people using indacaterol/glycopyrronium FDC after the 64-week trial than those taking glycopyrronium alone.¹⁰

People taking the FDC also reported greater improvements in health status (SGRQ) and less use of rescue medication compared with those taking glycopyrronium alone.¹⁰

The primary endpoint of the SPARK trial was number of exacerbations. Patients who had experienced a recent exacerbation requiring treatment with systemic corticosteroids and/or antibiotics. Severe exacerbation defined as hospitalisation, including emergency department visit >24 hours.¹⁰

---

¹ FEV₁ \( \text{AUC} \) (hours) is the area under the curve post bronchodilation divided by the number of hours and subtracting baseline FEV₁.

† The transition dyspnoea index (TDI) evaluates changes in dyspnoea over time and incorporates three components: functional impairment, magnitude of effort, and magnitude of task. The TDI focal score is the addition of scores from the three categories.¹³

§ The transition dyspnoea index (TDI) evaluates changes in dyspnoea over time and incorporates three components: functional impairment, magnitude of effort, and magnitude of task. The TDI focal score is the addition of scores from the three categories.¹³

II Moderate COPD exacerbation defined as requirement for treatment with systemic corticosteroids and/or antibiotics. Severe exacerbation defined as hospital admission, including emergency department visit >24 hours.¹⁰
Safety issues

The most common adverse events across the trials were typical complications of COPD, such as worsening COPD (including exacerbations), coughing, URTI or nasopharyngitis. The longest trial was the SPARK trial, with safety and efficacy data up to 64 weeks’ follow-up. There are no published safety data beyond 64 weeks.

For information about reporting adverse reactions to the Therapeutic Goods Administration, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine).

Comparable safety to that of both drugs delivered concurrently

In the BEACON trial, safety and tolerability of indacaterol/glycopyrronium FDC were equivalent to the profile for concurrent indacaterol 150 micrograms and glycopyrronium 50 micrograms delivered in separate inhalers over a 4-week period, with a similar percentage of people reporting adverse events (25.6% vs 25.2%). Nasopharyngitis, worsening COPD and a cough were the most common adverse events across both groups. The level of serious adverse events was equivalent between groups, and no deaths or cardiovascular or cerebrovascular events were reported in either group.

Safety of the FDC over concurrent delivery of both ingredients beyond 4 weeks has not been established.

No additive adverse effects from using this FDC bronchodilator

Safety and tolerability of indacaterol/glycopyrronium delivered as an FDC were comparable to that experienced in people using either component as a single agent, indicating there was no evidence of additive adverse effects when the two bronchodilators were delivered in a single inhaler.

COPD exacerbations, nasopharyngitis, cough and URTIs were the most common adverse events. However, because under the current PBS restriction patients must have been stabilised on the concomitant use of a LABA and a LAMA before being eligible for the FDC, if additive effects were experienced these would be addressed before starting on the FDC.

Caution in people with urinary retention, angle-closure glaucoma or renal failure

Due to the known risks of anticholinergics in people with angle-closure glaucoma or urinary retention, use caution if prescribing indacaterol/glycopyrronium FDC in these people.

Glycopyrronium is primarily eliminated by renal excretion. No dose adjustment is required for people with mild to moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2) but use with caution in people with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

Patients with urinary infections, angle-closure glaucoma or severe renal failure were excluded from clinical trials.

Be aware of paradoxical bronchospasm

As with any inhalation therapy, discontinue indacaterol/glycopyrronium FDC and switch to an alternative if the patient experiences paradoxical bronchospasm after inhalation.

Use with caution in people with cardiovascular disorders

As with all beta-2 agonists, use indacaterol/glycopyrronium FDC with caution in people with cardiovascular disorders (eg, coronary artery disease, acute MI, cardiac arrhythmias, hypertension), convulsive disorders or thyrotoxicosis, and those who are unusually responsive to beta-2 agonists, as these patients were excluded from clinical trials.

Use with caution in people with type 1 or uncontrolled type 2 diabetes

Plasma glucose level has been shown to increase after inhalation of beta-2 agonists, and people with type 1 or uncontrolled type 2 diabetes were excluded from the clinical trials.
Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee accepted that indacaterol/glycopyrronium FDC has a place in COPD therapy for patients already stabilised on individual components.

The PBAC noted concerns that the incremental benefit of the combination product on improving lung function could not be translated into clinically relevant measures of effect such as exacerbations and hospitalisations, but accepted that the combination may be more convenient and improve management of COPD while providing cost-savings for patients who are already using an individual LAMA and LABA in separate devices.

The Authority required (Streamlined) listing was imposed to address inappropriate prescribing of the product, particularly in the first-line setting.

Dosing issues

Administer indacaterol/glycopyrronium FDC capsules by oral inhalation using the Breezhaler device. 1

Dose once daily, preferably at the same time each day. If a dose is missed it may be inhaled as soon as possible but a double-dose is not required. Advise people taking indacaterol/glycopyrronium FDC not to take more than one dose per day. 1

Correct use of the inhaler is imperative. If patients do not report symptom improvement check inhaler technique before considering other options. 1 The correct inhaler technique is available online at NPS MedicineWise.

Information for patients

Explain to patients that, as maintenance treatment, the contents of one capsule of indacaterol/glycopyrronium FDC should be inhaled daily, even if the patient feels well.

Ensure the patient understands the difference between their maintenance treatment and reliever medicine and remind them to carry their reliever inhaler at all times.

Explain that indacaterol/glycopyrronium FDC capsules must be inhaled only with the Breezhaler device included with their medicines. Capsules are not to be swallowed.

Check the patient’s inhaler technique and ensure they understand how to use the device correctly (there are instructions on the inside of the packaging for Ultibro Breezhaler 110/50).

Medicines that are replaced by this FDC should be returned to a pharmacy for safe destruction.

Advise patients to store capsules in the blister pack to protect from moisture, and only remove immediately before use.

Arrange a follow-up appointment to occur 4 weeks after the patient starts indacaterol/glycopyrronium FDC to review control of the patient’s COPD.

Tell them to contact you if they find the usual dose of indacaterol/glycopyrronium FDC is not providing as much relief as their previous medications.

Tell the patient to stop taking Ultibro Breezhaler 110/50 and seek urgent medical attention if they experience:

- tightness in the chest, coughing, wheezing or breathlessness immediately after using the inhaler (signs of bronchospasm)
- difficulties breathing or swallowing, swelling of the tongue, lips or face, urticaria, skin rash (signs of hypersensitivity reaction)
- eye-pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes (signs of an acute attack of angle-closure glaucoma)
- pain or difficulty passing urine (signs of urinary retention).

Discuss the Ultibro Breezhaler 110/50 Consumer Medicine Information (CMI) leaflet with the patient.
REFERENCES


Date published: November 2014 (online); December 2014 (print)

Reasonable care is taken to provide accurate information at the time of creation. This information is not intended as a substitute for medical advice and should not be exclusively relied on to manage or diagnose a medical condition. NPS MedicineWise disclaims all liability (including for negligence) for any loss, damage or injury resulting from reliance on or use of this information.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.