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Inhaled therapy in chronic obstructive pulmonary disease (COPD)

This bulletin and supporting materials review medicines optimisation interventions for inhaled therapy in chronic obstructive pulmonary disease (COPD) ensuring that treatment is in line with national guidelines. Interventions discussed include the step down of inhaled corticosteroids (ICS) in COPD patients with mild to moderate severity, reviewing the place in therapy for the newer treatments and inhaler technique assessment.

The document refers to combination inhalers by the brand name.

Recommendations

- Ensure that when a patient is first prescribed an inhaler they are shown how to use it, they can demonstrate that they are able to use it and ensure inhaler technique is assessed on a regular basis to ensure correct ongoing technique. The PrescQIPP inhaler technique assessment support tools can be used by healthcare professionals to support inhaler technique assessment and provide written information to the patient on improving inhaler technique. Available at http://www.prescqipp.info/respiratory#inhaler-technique-assessment-tools
- Ensure all healthcare professionals checking inhaler technique are fully aware of how to use the inhalers and have their inhaler technique assessed regularly by peers.
- Optimise treatment of patients with COPD in line with national guidelines. Discontinue ineffective treatments before adding new ones.
- Consider the cost-effectiveness of treatments when prescribing for COPD. Suggested actions include:
  - Review patients on Seretide Evohaler® (unlicensed in COPD) for a switch to licensed Fostair® inhaler if a metered dose inhaler (MDI) (+ spacer) is deemed appropriate.
  - Formoterol Easyhaler® is the most cost effective long acting beta$_2$ adrenergic agonist (LABA). Consider a switch to formoterol Easyhaler® if an Easyhaler® is deemed appropriate.
  - DuoResp Spiromax® is a lower cost budesonide/formoterol alternative to Symbicort Turbohaler®. Consider a switch to DuoResp Spiromax® where appropriate, prescribing by brand and ensuring that the patient can demonstrate the correct inhaler technique.
- When prescribing a new medicine do not add it to the repeat template until effectiveness has been assessed after four weeks.
- Co-morbidities and interactions with other drugs may be affecting the patient's willingness or ability to use their medicines correctly. For patients with co-morbidities, consider whether treatment is optimal. For example:
  - For patients with eGFR ≤ 50 ml/min use aclidinium or umeclidinium as the preferred long acting muscarinic receptor antagonists (LAMAs).
  - For patients with diabetes consider whether a high dose ICS is worsening their condition (i.e. an increase in HBA1c seen after long term use of high dose ICS).
  - All LAMAs should be used with caution in patients with certain cardiovascular disease.

- Review patients on triple therapy. Only prescribe ICS for certain patients with moderate or severe COPD or patients with mild COPD and persistent exacerbations. When considering ICS in COPD, clinicians should weigh the possible benefits such as reduced exacerbations and improved quality of life, with the potential adverse effects, particularly an increased risk of pneumonia. Issue steroid warning cards to patients on high dose ICS.
- Identify patients with FEV1 ≥50% with less than two exacerbations in the last 12 months prescribed an ICS (as dual therapy or triple therapy). Where appropriate, consider a stepwise reduction of ICS whilst maintaining treatment with a bronchodilator or a combination of bronchodilators, i.e. LABA and LAMAs. Ensure that a multidisciplinary approach is adopted to carefully identify exacerbation risk and ensure regular review of patients when stepping down.
- For patients suffering adverse effects of high dose ICSs, consider discussion about alternative treatments including long acting bronchodilators.
- If the patient is being prescribed a short acting muscarinic antagonist (SAMA) as well as a LAMA, then discontinue the SAMA and ensure that all when required therapy is with a short acting beta agonist (SABA) such as salbutamol or terbutaline.
- For patients with a dual diagnosis of asthma and COPD, confirm correct diagnosis through symptoms and spirometry or refer to specialist for confirmation of diagnosis.
- Patients who have had asthma and have now developed COPD, step down asthma treatment in line with BTS asthma management guidelines when initiating treatment with a LAMA (to ensure that patients do not go straight onto triple therapy).
- Appropriate patients should be prescribed home rescue packs (steroids and antibiotics) to treat exacerbations - this has been shown to help prevent hospital admissions and is recommended in the National Institute for Health and Care Excellence (NICE) and Global initiative for chronic Obstructive Lung Disease (GOLD) clinical guideline on COPD as part of self-management of exacerbations.[1,2]

Supporting evidence

COPD is a long term progressive condition characterised by persistent airflow obstruction that is not fully reversible. People with COPD have difficulties breathing and the most common symptoms are increasing breathlessness when active and a persistent cough with phlegm. COPD is predominately caused by smoking but other factors, particularly occupational exposure (fumes, dust and genetic disorders) may also contribute to the development of the disease. COPD can lead to severe symptoms, disability and impaired quality of life. Exacerbations often occur, when there is a rapid and sustained worsening of symptoms beyond normal day to day variation. Reported symptoms are increased breathlessness, cough, sputum volume, sputum purulence, wheeze, malaise/fatigue and temperature. Management involves increased frequency of bronchodilator use, antibiotics and/or steroids. Some exacerbations may require hospitalisation.[1,2]

According to GP QoF registers, from April 2013 to March 2014 there were 1,004,920 patients in the UK with COPD (prevalence of 1.78%).[3] In 2013 there were more than 27,000 deaths in England and Wales attributable to COPD; the majority of these were in the 75-84 age range.[3] During 2012/13 there were approximately 117,800 hospital admissions in England where COPD was the primary diagnosis.[4]

Population studies indicate that among patients hospitalised for COPD, 50% are subsequently re-admitted. In total, 60% of COPD patients report limitations with activities of daily living, with 45% being unable to work.[5] The management of patients with stable COPD should be aimed at control of symptoms, prevention of exacerbations and improvement in exercise capacity.[6] The direct NHS cost of treating COPD and exacerbations is over £800 million each year.

National guidelines

The NICE clinical guideline for COPD (CG101) was published in 2010. A surveillance review (which checked the need to update CG101) was undertaken in July 2014 and a decision was made not to update the clinical guideline. The next update is expected in June 2016. There have been several new inhalers launched since July 2014 which include branded generic ICS/LABA combination inhalers, new LAMA inhalers and the LABA/LAMA combination inhalers.

The current guidelines recommend that in people with stable COPD who remain breathless or have exacerbations, despite use of short-acting bronchodilators as required, have the following considered as maintenance therapy:[1]

- If FEV1 is ≥50% predicted, use either a LAMA or LABA.
- If FEV1 is <50% predicted, use either a LABA with an ICS in a combination inhaler, or a LAMA. If an ICS cannot be tolerated, then a LABA plus LAMA combination is an alternative.

In patients with persistent exacerbations or breathlessness, various combinations are advised, including a LAMA in addition to a LABA plus ICS.

The NICE Quality Standard defines best clinical practice within thirteen standards for the assessment, diagnosis and management of patients with COPD.[7] These include offering support to stop smoking, a key intervention that has been shown to reduce the rate of decline in lung function.

GOLD updated their global strategy for diagnosis management and prevention of chronic obstructive pulmonary disease in January 2015. The guidelines classify patients according to their degree of FEV1 severity, more/less symptoms, quality of life and exacerbation history.[2]

For patients with significant symptoms but a low risk of exacerbations, a LAMA or LABA is recommended. The alternative choice for severe breathlessness is a combination of a LABA plus LAMA.

In patients with few symptoms and a high risk of exacerbations, an ICS plus LABA or a LAMA is recommended; a LABA plus LAMA is an alternative option.

For patients with significant symptoms and high risk of exacerbations, triple therapy (ICS plus LABA plus LAMA) is recommended. A combination of a LABA and LAMA is also recommended as an alternative option to triple therapy in these high risk patients.

Summaries of the NICE and GOLD guidelines are illustrated in attachments 1a and 1b, http://www.prescqipp.info/inhaled-therapy-in-copd/viewcategory/191

Treatment options for COPD

Misdiagnosis of COPD is very common and means that patients are not on optimal treatment.[8,9] Suboptimal prescribing or adherence will affect the patient's ability to self-manage, their use of primary care, A&E, secondary care and the cost of medicines. Audit tools, e.g. GRASP-COPD are available to assist GP practices to interrogate their clinical data.[10] Available at https://www.nottingham.ac.uk/primis/tools-audits/tools-audits/grasp-suite/grasp-copd.aspx

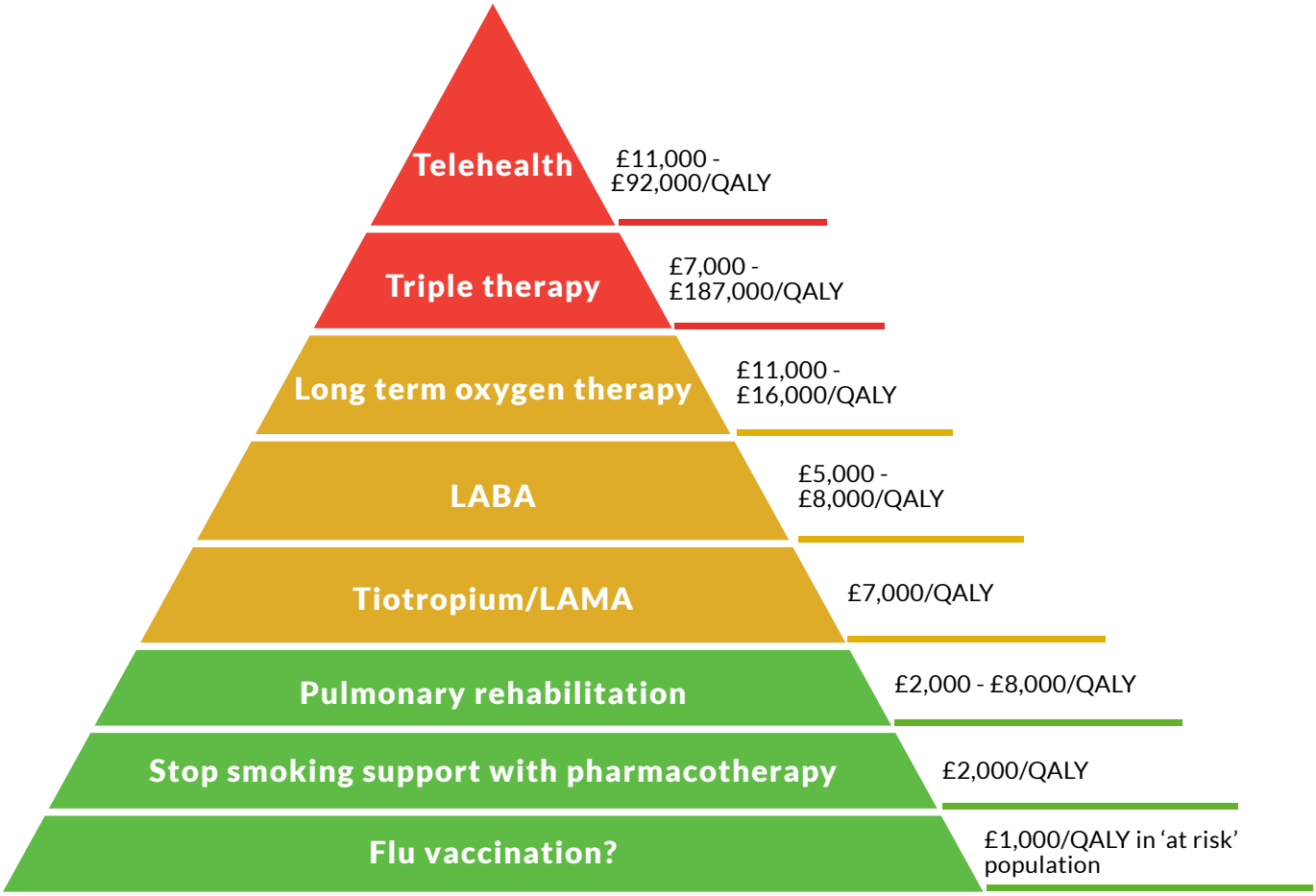
Non adherence is estimated at between 30 – 70% of which up to 50% may be deliberate, and 30% or more of patients may be on sub optimal therapy for the severity of their disease.[11] Ensuring that medicines are clinically appropriate, cost effective and acceptable to the patient can reduce waste, save money and improve outcomes for patients. Inhaler technique should also be assessed regularly to ensure that patients get the best out of their prescribed medicines.

Non-drug interventions

Non-drug interventions and lifestyle advise such as stopping smoking, flu vaccination and pulmonary rehabilitation more cost effective than COPD drug treatments and these measures should be offered and uptake maximised in all COPD patients. Ensuring that these measures are being used will ultimately

reduce expenditure on prescribing as patients will be better managed. Patient education and self care are also key components of COPD management.

In 2013, The London Respiratory Team updated their value pyramid for COPD highlighting the relative costs per QALY for COPD treatments and interventions.[12] The cost/QALY for triple therapy in COPD (i.e. an ICS plus LAMA plus LABA) is between £7,000 and £187,000, the upper limit of which is well above the NICE threshold of £21,000 per QALY for a treatment to be regarded as cost effective. The diagram shown below is an adaptation of this pyramid. Telehealth is not a cost effective intervention and accumulating data from a variety of studies indicate that telehealth in any of its current forms has not shown benefits for patients with COPD; thus, telehealth is not recommended for use with COPD patients.[7] Of note is that this pyramid predates the licensing of LABA/LAMA combinations.



Inhaled therapies

There has been a plethora of new treatments that have emerged onto the market and their place in therapy with a summary of evidence is discussed in the relevant sections below. All newer products lack patient–orientated outcome data beyond 52 weeks. NICE evidence summaries are available for all new products.

Table 1, on page 6, shows the monthly costs for different treatments licensed to treat COPD as well as the maximum and minimum costs for using LAMA plus LABA and triple therapy.

Cost differences within a class have been calculated for the different products and organisations can use these calculations to apply to their own data to calculate potential savings if a switch to a certain product is being considered.

It would also be beneficial to review the patients on combinations of treatment that are not considered cost effective and optimise their medicines. The audit (attachment 2. COPD audit) available with this bulletin will support this work. It is important when changing medication for COPD patients to consider the risk of an exacerbation (particularly for products containing an inhaled corticosteroid) and educate/ support the patient in managing these with additional use of their SABA inhalers or rescue medicines

as required. It is also important to ensure all key stakeholders are involved and have agreed to the selected interventions. Getting their agreement to make these changes to medication will ensure that any projects undertaken run smoothly. Key stakeholders would include respiratory consultants and respiratory nurses. Community pharmacists should be informed of any planned changes so that they can help the patient with advice and support as necessary.

The choice of inhaler will depend on the ability of the patient to use the inhaler. Individual patient assessment is needed. Delivery of newer drugs are through novel drug delivery devices and it is paramount that inhaler technique is correct, inspiratory flow rates checked and re-checked at each visit. Some COPD patients may find it difficult to achieve the correct inspiratory flow rate needed for some of the dry powder, breath actuated inhalers.

Table 2 (page 11) highlights the different devices and key points on their usage. PrescQIPP inhaler technique assessment tools provide information on using different inhalers available at http://www.prescqipp.info/respiratory#inhaler-technique-assessment-tools

Table 1: Inhaler choices and costs in COPD (all doses are expressed as metered doses unless stated)

* Note. All LAMAs and LABAs (including combination therapies) cautioned in cardiovascular disease. See SPC for full details

Drug name	pMDI (+ spacer) (see table 2)	Dry powder	Dose	Comments*	Cost per 30 days or per inhaler for "prn" doses [13,14]	Cost difference available from cheapest in class (excluding prn)
SABAs						
Salbutamol®	Salbutamol® 100mcg/dose		2 inhalations prn		£1.50 /200 doses	-
		Ventolin 200mcg/dose Accuhaler®	2 inhalations prn		£3.00 /60 doses	-
		Salbutamol 100mcg/ dose Easyhaler®	2 inhalations prn		£3.31 /200 doses	-
Terbutaline®		Bricanyl 500mcg Turbohaler®	2 inhalations prn		£6.92/100 doses	-
SAMAs						
Ipratropium®	Atrovent® 20mcg/dose inhaler®		1-2 inhalations prn		£5.56/200 doses	-
LABAs						
Formoterol®		Formoterol 12mcg Easyhaler®	One inhalation twice daily		£11.88	-
	Atimos® 12mcg inhaler		One inhalation twice daily (up to four puffs daily)		£18.04 - £36.08	34% (if one inhalation twice daily)
		Foradil 12mcg Aerolizer®	One inhalation twice daily		£23.38	48%
		Oxis Turbohaler® 6mcg and 12mcg	One inhalation once daily or twice daily		£29.26	59%

Drug name	pMDI (+ spacer) (see table 2)	Dry powder	Dose	Comments*	Cost per 30 days or per inhaler for "prn" doses [13,14]	Cost difference available from cheapest in class (excluding prn)
LABAs continued						
Salmeterol	Serevent® 25mcg Evohaler®		Two inhalations twice daily		£29.26	59%
		Serevent®50mcg Accuhaler®	One inhalation twice daily		£29.26	59%
Indacaterol		Onbrez® 150mcg/300mcg Breezhaler®	One inhalation daily		£29.26	59%
Olodaterol [15]	Striverdi® 2.5mcg/dose Respimat®		Two inhalations once daily	Limited experience in severe renal impairment	£26.35	55%
LAMAs						
Glycopyrronium[16]		Seebri® 50mcg Breezhaler®▼	One capsule inhalation daily	Caution when eGFR<30ml/min	£27.50	-
Umeclidinium[17]		Incruse® 55mcg Ellipta®▼	One inhalation daily	Expires 6 weeks after opening	£27.50	0%
Aclidinium[18]		Eklira® 300mcg Genuair ®▼	One inhalation twice daily		£28.60	4%
Tiotropium[19]		Spiriva® 18mcg Handihaler®	One inhalation daily	Caution when eGFR <50ml/min	£34.87 30 doses (including Handihaler) £33.50 30 doses refill	18% (if refill)

Drug name	pMDI (+ spacer) (see table 2)	Dry powder	Dose	Comments*	Cost per 30 days or per inhaler for "prn" doses [13,14]	Cost difference available from cheapest in class (excluding prn)
Tiotropium[20]	Spiriva® 2.5mcg Respimat®		Two inhalations once daily	Caution when eGFR <50ml/min	£33.50	18%
LABA/LAMA combination inhalers						
Umeclidinium/ vilanterol[21]		Anoro® 55/22 mcg Ellipta®▼	One inhalation daily		£32.50	0%
Aclidinium/ formoterol[22]		Duaklir® 340/12 Genuair®▼	One inhalation twice daily		£32.50	0%
Indacaterol/ glycopyrronium [23]		Ultibro 110/50mcg Breezhaler®▼	One capsule inhalation daily	With severe renal impairment or end stage renal dialysis only use if the expected benefit outweighs the risk.	£32.50 (including inhaler)	0%
Tiotropium/ olodaterol[24]	Spiolto® 2.5/2.5mcg Respimat® Soft Mist™		Two inhalations once daily	Caution when eGFR <50ml/min	£32.50	0%
Individual components used together (min – max cost)					£39.38 - £64.13	(17% - 49%)

Drug name	pMDI (+ spacer) (see table 2)	Dry powder	Dose	Comments*	Cost per 30 days or per inhaler for "prn" doses [13,14]	Cost difference available from cheapest in class (excluding prn)
ICS/LABA – Not an automatic step up for the treatment of breathlessness in COPD ++ Licensed indication: Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.						
Fluticasone furoate/ vilanterol[25]		Relvar® 92/22 Ellipta® (Delivered dose▼ (++FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.)	One inhalation daily	Expires 6 weeks after opening. Fluticasone furoate is approximately equivalent to fluticasone propionate 250mcg bd. However direct comparator studies have not been published.	£27.80	0%
Beclometasone extrafine/ formoterol[26]	Fostair® 100/6 inhaler (++FEV1 < 50% predicted normal)		Two inhalations twice daily	Contains a small amount of ethanol: 7mg/actuation.	£29.32	5%

Drug name	pMDI (+ spacer) (see table 2)	Dry powder	Dose	Comments*	Cost per 30 days or per inhaler for "prn" doses [13,14]	Cost difference available from cheapest in class (excluding prn)
ICS/LABA – Not an automatic step up for the treatment of breathlessness in COPD ++ Licensed indication: Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.						
Budesonide/ formoterol		DuoResp® Spiromax® 320/9 or 160/4.5 (Delivered dose) (++FEV1 < 50% predicted normal)[27]	320/9 – One inhalation twice daily 160/4.5 – Two inhalations twice daily	PRESCRIBE BY BRAND NAME	£29.97	7%
		Symbicort ® Turbohaler® 400/12 (++FEV1 < 50% predicted normal)[28]	One inhalation twice daily	PRESCRIBE BY BRAND NAME	£38	27%
Fluticasone propionate/ salmeterol		Seretide® Accuhaler® 500/50 (++FEV1 < 60% predicted normal, (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.)[29]	One inhalation twice daily		£40.92	32%
Triple therapy – ICS/LABA plus LAMA: Individual components (min – max cost)					£55.30 -£75.79	

Table 2: Drug delivery devices. Also see SPC and PILs at www.medicines.org.uk

Drug name	Device (If MDI + spacer use options a, b, c)	Dose counter	Dose check	Preloaded	Warning when close to empty (Red)	Pack size	Optimal inspiratory flow rate l/min (contact with manufacturers or SPC)	Cost per Month (Drug Tarifff/MIMS Oct 2015)[13,14]
LABA								
Formoterol[30]	Easyhaler®	Yes	Lactose taste	Yes	Last 20	120	28	£11.88
Formoterol[31]	MDI (a)	No	Propellant taste	Yes	No	100	<30	£18.36
Salmeterol[32]	MDI (a,b,c)	No	Propellant taste	Yes	No	120	<30	£29.26
Salmeterol[33]	Accuhaler®	Yes	Visual/lactose taste	Yes	Last 5	60	30-90	£29.26
Indacaterol[34]	Breezhaler®	No	Audible/lactose taste	No	N/A	30	50	£29.26
Olodaterol[15]	Respimat®	Yes – scale with pointer	No information	Yes	Last 14	60	Independent of inspiratory effort	£26.35
LAMA								
Glycopyrronium[16]	Breezhaler®	No	Audible/ lactose taste/ visual and empty capsule	No – single capsules	N/A	6 or 30	50	£27.50
Umeclidinium[17]	Ellipta	Yes	Audible/visual	Yes	Last 9	30	42-128	£27.50
Aclidinium[18]	Genuair®	Yes –in 10s	Audible/visual/ lactose/sweet taste	Yes	Last 10	60	35 -90	£28.60
Tiotropium[19]	Handihaler®	No	Capsule vibration	No	N/A	30	20 – 30	£33.50
Tiotropium[20]	Respimat®	Yes – scale with pointer	No information	Yes	Last 14	60	Independent of inspiratory effort	£33.50
LABA/LAMA								
Umeclidinium/ vilanterol (Anoro®)[21]	Ellipta®	Yes	Audible/visual	Yes	Red – last 9 doses	30	43 - 124	£32.50

Drug name	Device (If MDI + spacer use options a, b, c)	Dose counter	Dose check	Preloaded	Warning when close to empty (Red)	Pack size	Optimal inspiratory flow rate l/min (contact with manufacturers or SPC)	Cost per Month (Drug Tarifff/MIMS Oct 2015)[13,14]
LABA/LAMA								
Aclidinium/formoterol (Duaklir®)[22]	Genuair®	Yes – in 10s	Audible/visual/ slightly sweet or bitter taste	Yes	Last 10	60	35	£32.50
Indacaterol / glycopyrronium bromide (Ultibro®)[23]	Breezhaler®	No	Audible/ lactose taste/ Visual and empty capsule	No	N/A	12 or 30	50	£32.50
Tiotropium/olodaterol (Spiolto®)[24]	Respimat®	Yes – scale with pointer	No information	Yes	Last 14	60	Independent of inspiratory effort	£32.50
ICS/LABA								
Beclometasone/ formoterol (Fostair®)[26]	MDI (a,b)	No	Propellant taste	Yes	No	120	<30	£29.32
Budesonide/ formoterol (DuoResp®)[27]	Spiromax®	Yes	Audible/visual/ lactose	Yes	Last 20	60 or 120	40 – 60	£29.97
Budesonide/ formoterol (Symbicort®)[28]	Turbohaler®	Yes	Lactose	Yes	Locks cap at zero	60	60 – 90	£38.00
Fluticasone propionate/salmeterol (Seretide®)[29]	Accuhaler®	Yes	Visual/lactose taste	Yes	Last 5	60	>30	£40.92
Fluticasone furoate/ vilanterol (Relvar®)[25]	Ellipta®	Yes	Audible/visual	Yes	Last 9	30	43 – 129	£27.80

a = A2A Spacer, Able Spacer, Compact Space Chamber Plus, Fisio Chamber Vision, Flo-Tone MDI, Optichamber Diamond, Pocket Chamber, Space chamber plus and vortex b =Aerochamber plus c = Volumatic

Bronchodilators

LAMA or LABA inhalers have an important and established role to play in the management of COPD. LABAs and tiotropium (the only established LAMA on the market) have been shown to significantly reduce the risk of patient-oriented outcomes such as COPD exacerbations.[1] There is no evidence to recommend one class of long acting bronchodilators over another for initial treatment in patients with low risk of exacerbations and more symptoms of breathlessness.[2]

Long acting muscarinic receptor antagonist (LAMA) inhalers

A LAMA inhaler is an option for treatment for either part of the NICE guidance treatment pathway for COPD, i.e. where FEV1 is ≥50% or <50%. If a patient is on a LABA and FEV1<50%, consider a switch to a LAMA in line with NICE and GOLD guidance.[1,2]

If a patient is using a SAMA, this should be discontinued before a LAMA is prescribed.

There are four LAMA inhalers currently available:

- Tiotropium
- Aclidinium
- Glycopyrronium
- Umeclidinium.

All are taken once daily except aclidinium which is taken twice daily.

The most commonly reported adverse events are generally consistent with complications of COPD and use of anticholinergics. In studies, the rates of adverse events for aclidinium and glycopyrronium such as dry mouth and constipation, were low overall (<2%) and similar in the treatment and placebo arms.[16,18] Local adverse effects due to drug delivery may include throat irritation, nasopharyngitis, rhinitis and sinusitis. All LAMAs are cautioned in patients in certain cardiovascular disease. Class effects of LAMA such as paradoxical bronchospasm, anticholinergic activity, cardiovascular and cerebrovascular events should be monitored along with the potential risk of lower respiratory tract infection.

LAMAs should also be used with caution in people with risk factors for angle-closure glaucoma or prostatic symptoms. Acute angle-closure crisis and urinary retention are known adverse effects associated with anticholinergics. Advise patients to be alert to symptoms indicating these conditions.[16-19]

With aclidinium and umeclidinium, no dosage adjustment and no additional monitoring in renal impairment is required.[17,18]

Updated GOLD guidelines state that aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium, whereas far less data are available for other outcomes.[2]

The NICE evidence summaries for the individual therapies state that more robust evidence comparing patient-orientated outcomes for newer treatments with other active treatments for COPD would enable their place in therapy to be more clearly established. Local decision makers will need to consider the evidence for these drugs alongside that for the other treatments for COPD. Individual patient factors and the costs and safety profile of each treatment will need to be taken into account. The Scottish Medicine Consortium (SMC) has accepted the newer LAMAs, aclidinium, glycopyrronium and umeclidinium (along with tiotropium Respimat and Handihaler) for use in Scotland.[35-37]

Tiotropium powder 18mcg/inhalation and tiotropium 2.5mcg/puff solution for inhalation (Spiriva Handihaler®, Spiriva Respimat®)

- Tiotropium improves lung function, quality of life, exercise endurance and reduces exacerbations.[38-41]
- A Cochrane systematic review documented that the number needed to treat (NNT) with tiotropium over the course of one year to prevent one additional exacerbation was 16.[42] There has been past concern that tiotropium delivered via the Respimat® device was associated with a significantly

increased risk of mortality compared with placebo.[43] However the findings in the TIOSPIR trial showed that there was no difference in mortality or rates of exacerbation when comparing tiotropium in a dry powder inhaler, Handihaler® to the Respimat® inhaler. The incidences of different causes of death (including death due to cardiovascular events) and incidences of major cardiovascular adverse events were similar across the three groups. There was no significant difference in the risk of the first exacerbation of COPD and in participants with previous cardiac arrhythmia there was no significant difference in the risk of death from any cause between tiotropium Respimat® 5 micrograms and tiotropium HandiHaler® 18 micrograms.[44] A recent Drug Safety Update states that when using tiotropium delivered via Respimat® or Handihaler® to take the risk of cardiovascular side effects into account for patients with conditions that may be affected by the anticholinergic action of tiotropium, including:

- Myocardial infarction in the last six months,
- Unstable or life threatening cardiac arrhythmia,
- Cardiac arrhythmia requiring intervention or a change in drug therapy in the past year,
- Hospitalisation for heart failure (NYHA Class III or IV) within the past year.

It also states to tell these patients to report any worsening of cardiac symptoms after starting tiotropium; patients with these conditions were excluded from clinical trials of tiotropium, including TIOSPIR. Review the treatment of all patients already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of patients at high risk of cardiovascular events.[45]

- The patent for tiotropium is expected (including an extension of the paediatric licence) to expire in March 2016.[46]

Aclidinium bromide 322 microgram (delivered dose) inhaler (Eklira Genuair®)

- Aclidinium bromide differs from tiotropium by its higher selectivity for M3 muscarinic receptors with a faster onset of action.[18]
- Evidence from two phase III placebo-controlled trials (ACCORD COPD I [n=561, 12 weeks] and ATTAIN [n=828, 24 weeks]) in patients with moderate to severe COPD showed that aclidinium bromide 400 micrograms improved FEV1 over 12 and 24 weeks compared to placebo. Improvement in trough FEV1 in ACCORD was 124 ml, and in ATTAIN was 128 ml, which is clinically relevant (these differences are around the level considered to be clinically relevant (minimum clinically important difference 100 ml as stated by NICE).[47]
- In the 24-week study, more patients had clinically significant improvements in the patient-orientated secondary outcomes of health status (St George's Respiratory questionnaire score, SGRQS) and transitional dyspnoea index (TDI) scores with aclidinium bromide than with placebo.[47]
- Further to this, a Cochrane review of 12 studies (of 9547 patients) over 52 weeks showed that aclidinium 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.[48]
- Based on published data, the effects of aclidinium bromide on lung function appear to be comparable to tiotropium. However, it has not been directly compared with tiotropium or LABAs. Additional trials are recommended to assess the efficacy and safety of aclidinium compared to other LAMAs or LABA.[47]
- There is insufficient published evidence to support a switch in prescribing from tiotropium to aclidinium bromide in patients already receiving treatment for COPD.

Glycopyrronium dry powder 55 microgram (delivered dose) inhaler (Seebri Breezhaler®)

- Glycopyrronium dry powder inhaler is a once daily inhaled LAMA administered using a single-dose dry powder inhaler, the Breezhaler®.
- Evidence from two phase III placebo-controlled studies (GLOW1 [n=822, 26 weeks] and GLOW2 [n=1066, 52 weeks]) in patients with moderate to severe COPD, showed a statistically significant improvement in the disease-oriented primary end point, 12-week trough FEV1 with glycopyrronium bromide compared with placebo (least squares mean difference 108 ml and 97 ml respectively, both p<0.001). In both studies, a statistically significant difference was seen for the key secondary patient-oriented outcomes, breathlessness (TDI) and health status (SGRQ). However, the effect sizes for these measures were small. The difference considered to be clinically important for health status was not reached in GLOW1 or GLOW2. For breathlessness, the difference considered to be clinically important was achieved in GLOW1 but not in GLOW2. GLOW2 included an open-label comparison with tiotropium and showed similar results to glycopyrronium bromide with no statistically significant difference between treatment for TDI and SGRQ.[49] A blinded glycopyrronium and tiotropium study, GLOW 5, showed efficacy and safety results consistent to GLOW2.[50]
- GLOW3, a small 108 patient study showed an improvement in exercise tolerance after three weeks.[51] In GLOW5 and in a pooled analysis of GLOW1 and GLOW2 data, both glycopyrronium and tiotropium were comparable in delaying patients' first moderate or severe exacerbation and in their use of rescue medication.[52]
- No studies have been conducted comparing aclidinium and glycopyrronium. A systematic review and network meta-analysis of these long-acting anticholinergics suggests they have similar therapeutic effects.[53,54]
- Glycopyrronium can be used at the recommended dose in patients with mild to moderate renal impairment, eGFR > 30ml/min.[16]

Umeclidinium inhalation powder 55 microgram (delivered dose) (Incruse Ellipta®)

- Umeclidinium was recently launched in October 2014. It is presented in a pre-loaded Ellipta® device.
- Evidence from two randomised controlled trials (RCTs) have shown that umeclidinium 55 micrograms improved FEV1 by 0.127 litres (127ml) (1 RCT; n=206; 12 weeks) and 0.115 litres (115ml) (1 RCT; n=1536; 24 weeks) compared with placebo in patients with moderate to severe COPD. There was also improvement in symptomatic outcomes such as dyspnoea; 1.0 unit with umeclidinium compared with placebo (1 RCT; n=1536; 24 weeks). No statistically significant difference between umeclidinium and placebo for TDI score in the 12-week RCT (1 RCT; n=206; 12 weeks).[55]
- There are no published studies, which directly compare umeclidinium 55 micrograms with a currently available LAMA or LABA.
- There are limited long-term efficacy and safety data for the licensed dose. A post-authorisation observational safety study will compare umeclidinium and tiotropium for the incidence and comparative safety of selected cardiovascular and cerebrovascular events and lower respiratory tract infections including pneumonia in people with COPD.[56]
- The SMC noted that there is no direct comparative evidence of umeclidinium with other LAMAs. However, results of three adjusted indirect comparisons of umeclidinium versus tiotropium, aclidinium and glycopyrronium showed that there was no significant difference in lung function at 24 weeks (measured as FEV1), SGRQ, TDI and rescue medication at 12 and 24 weeks. The data is limited due to heterogeneity. Further to this, the SMC used a cost minimisation analysis to compare the drug acquisition costs only. Umeclidinium 55 micrograms was demonstrated to represent cost savings compared to tiotropium and aclidinium, and to be cost neutral compared to glycopyrronium.[37]

In terms of preferred choice, CCGs and prescribers are advised to take into account inhaler device, individual patient factors and cost along with the available evidence.

Long acting beta$_2$ adrenergic agonist (LABA) inhalers

LABA inhalers have been shown to improve patient orientated outcomes such as exacerbations in COPD. They can be used as monotherapy in COPD patients with an FEV1 of at least 50% as an alternative to LAMA drugs. LABA drugs significantly improve FEV1 and lung volumes, dyspnoea, health related quality of life and exacerbation rate but have no effect on mortality and rate of decline of lung function.[1,7] If a patient is on a LABA with severe disease, consider a switch to a LAMA in line with NICE and GOLD guidance.[1,2]

There are currently four LABA inhalers on the market. Salmeterol and formoterol are both established twice daily inhalation treatments. Formoterol Easyhaler® is currently the lowest acquisition cost LABA product on the market.[13]

Indacaterol is a newer once-daily LABA also delivered via the Breezhaler® device. Evidence from studies of up to 12 months duration has demonstrated superior efficacy compared with placebo, although similar efficacy to formoterol and tiotropium. Indacaterol has a lack of long-term safety data, a significantly higher cost than twice-daily alternatives and no evidence supporting an improvement in patient orientated outcomes.[57]

Olodaterol 2.5 microgram (delivered dose) solution for inhalation (Striverdi Respimat®)

- Olodaterol was launched in June 2014. Olodaterol is a once daily solution delivered through the Respimat® inhaler.
- Results of two 48 week RCTs (n=904 and n=934) demonstrated that the FEV1 area under the curve from 0-3 hours response after 24 weeks showed a 151ml and a 129 ml improvement for olodaterol vs. placebo. Changes in FEV1 were comparable to formoterol. However the improvements in trough FEV1 (range 53ml to 78ml) seen with both drugs was less than the 100ml that the full NICE guideline on COPD considers to be clinically important.[58]
- Statistically significant improvements in health-related quality of life were seen with olodaterol compared with placebo.[58]
- The results were less conclusive for dyspnoea and the difference for olodaterol compared with placebo is less than the one unit that the full NICE guideline on COPD considers to be clinically important. The studies were not designed to assess exacerbations.[58]
- The olodaterol studies permitted the use of concomitant pulmonary medications (LAMAs, short-acting muscarinic antagonist, xanthines and inhaled corticosteroids). The studies may not reflect clinical practice where LABAs are used alone in line with NICE guidance.[58]
- No significant improvement was observed with either olodaterol or formoterol, in relation to the number of exacerbations experienced.[58]
- There is no data regarding the effect of olodaterol on hospitalisation rates.
- There is no direct comparative data with salmeterol; indirect comparisons showed no significant difference between olodaterol and salmeterol in trough FEV1 at six months or in the relative risk of experiencing an adverse event, and a significant difference in SGRQ total score in favour of olodaterol for the LAMA free population only.[59]
- The adverse effect profile appears to be in line with other LABAs.
- There is limited long term safety data beyond 48 weeks treatment and in patients with cardiovascular disease, hepatic impairment or severe renal impairment.[15]
- There are currently no ICS/olodaterol combination products available, which will complicate switching patients between olodaterol monotherapy and combined preparations.
- Following resubmission, the SMC accepted the use of olodaterol within NHS Scotland.[59]

Long acting beta$_2$ agonist (LABA)/long acting muscarinic antagonist (LAMA) combination inhaler (LABA/LAMA combinations)

- These combinations are licensed as maintenance bronchodilator treatment to relieve symptoms in adults with COPD. There are now four LABA/LAMA combinations (given via a single device) available:
  - Indacaterol/glycopyrronium (Ultibro Breezhaler®)
  - Umeclidinium/vilanterol (Anoro Ellipta®)
  - Aclidinium/formoterol (Duaklir Genuair®)
  - Tiotropium + olodaterol (Spiolto Respimat®).
- GOLD guidelines state that the combined use of short or long acting beta$_2$ agonists and anticholinergics may be considered if symptoms are not improved with single agents.
- The combined use of LAMA and LABA may be an alternative option to a LAMA or LABA in patients with severe breathlessness symptoms (Group B patients – see attachment 1b). GOLD also recommends a LAMA + LABA combination as an alternative option to combined ICS with LABA or LAMA, in patients with few symptoms but a high risk of exacerbations or high symptoms and a high risk of exacerbations (Group C and D patients - see attachment 1b).
- GOLD guidelines state that good clinical evidence for combining long acting bronchodilators in patients with high risk of exacerbations is lacking; they show a significant increase in lung function whereas the impact on patient reported outcomes is still limited. **There is still too little evidence to determine if a combination of long acting bronchodilators is more effective than a long acting anticholinergic alone for preventing exacerbations.**[2]
- Whilst NICE states that the current place in therapy of a combination LABA/LAMA is unclear, it also states that use of dual therapy with a LAMA and LABA may be considered if an ICS (as part of combination therapy with a LABA) is declined or not tolerated.[1]
- All four LABA/LAMA combinations improve lung function compared with placebo and their individually licensed components. However the improvements are small and less than the threshold that NICE considers to be clinically meaningful.[24,60-62]
- The Midlands Therapeutics Review and Advisory Committee (MTRAC) considered that there was currently insufficient patient-oriented RCT evidence available to draw distinctions between the different products or make comparisons with LABA/ICS inhalers.[63]
- The SMC has accepted the use of the first three LABA/LAMAs.[64-66] Spiolto Respimat® is scheduled for review in November 2015.
- Compared with established LABAs and LAMAs the comparative efficacy and long-term safety on LAMA and LABA combinations is unclear, particularly in terms of reducing exacerbations.[60]
- In clinical trial designs, patients with cardiovascular disease were excluded from studies, so all the four LABA/LAMA combinations are cautioned in cardiovascular disease to different degrees.[24,60-62]
- In renal impairment, no dosage adjustment is required for Duaklir Genuair® or Anoro Ellipta®. Spiolto Respimat® should be used with caution in patients with moderate to severe impairment (creatinine clearance ≤50 ml/min); there is no long term experience in patients with severe renal impairment.[21,22,24] In patients with severe renal impairment or end-stage renal disease requiring dialysis, Ultibro Breezhaler® should be used only if the expected benefit outweighs the potential risk.[23]
- In hepatic impairment, no dosage adjustment is required for Duaklir Genuair® . Whilst Ultibro Breezhaler®, Anoro Ellipta® and Spiolto Respimat® can be used at the recommended dose in patients with mild and moderate hepatic impairment, there are no data available for their use in severe hepatic impairment; therefore caution should be observed in these patients.[21-24]

- All combination inhalers are less costly than the combined costs of the single inhalers and may be more convenient for patients.[13,14]

Indacaterol/glycopyrronium 85/43 micrograms (Ultibro Breezhaler®)

This combination was launched in December 2014 and is the first LABA + LAMA combination inhaler to be approved for COPD. Like glycopyrronium it is delivered through the Breezhaler® device where capsules need to be loaded into the device; the Breezhaler® device is known to have a lower inspiratory resistance than the Accuhaler®, Handihaler® and Turbohaler® devices.[67]

- Efficacy data for two large studies, (SHINE - 26 weeks, moderate to severe COPD; SPARK-64 weeks, severe or very severe COPD) showed Ultibro Breezhaler®significantly improved bronchodilatation compared to its individually licensed components. The clinical relevance in relation to other active comparators is unclear. In SHINE, Ultibro Breezhaler® statistically significantly improved trough FEV1 compared with its individual components, open-label tiotropium and placebo (differences 70ml, 90ml, 80ml and 200ml respectively; p<0.001 in all comparisons). For comparisons with active comparators, these changes in FEV1 are less than the 100 ml or more that the NICE considers to be clinically important.[61]
- Ultibro Breezhaler® also showed small statistically significant improvements in dyspnoea, health status and use of rescue medication compared with active comparators, which were of uncertain clinical benefit.[61]
- Statistically significant improvements in moderate to severe exacerbations were observed when compared with glycopyrronium monotherapy (rate reduction of 12% compared to glycopyrronium, p=0.038). A non-significant reduction of 10% was seen in this secondary outcome between Ultibro Breezhaler® and open-label tiotropium (p=0.096). Ultibro Breezhaler® treated patients also had the lowest rate of moderate or severe COPD exacerbations per year compared to glycopyrronium bromide and tiotropium (0.94, 1.07 and 1.06, respectively). Based on this rate, the number needed to treat to prevent one additional moderate or severe exacerbation over a year in the Ultibro Breezhaler® group was 8 vs. glycopyrronium bromide and 9 vs. tiotropium.[68]
- The ILLUMINATE study in people with moderate to severe COPD reported that Ultibro Breezhaler® was superior to Seretide® in improving bronchodilatation in moderate to severe COPD, however more data is required before a definitive conclusion can be determined.[61]
- The BLAZE study (n=247) in people with moderate to severe COPD found that Ultibro Breezhaler® statistically significantly improved dyspnoea scores in people with moderate or severe COPD compared with placebo. The mean difference exceeded the 1 point improvement considered to be clinically important. The dyspnoea score for Ultibro Breezhaler® was also statistically significantly higher than for tiotropium (difference 0.49; p=0.021). However, this difference is unlikely to be clinically important.[61]
- The SPC for Ultibro Breezhaler® reports that up to 15 months' treatment showed similar adverse reactions to those observed when people were treated with each drug individually.[23]

Umeclidinium/vilanterol 52/22 (Anoro Ellipta®)

- Anoro Ellipta® is a multi-dose, dry powder combination inhaler containing a LAMA and LABA delivered via the Ellipta device. Administration is also once daily.
- The combination inhaler has been compared in three RCTs in moderate to very severe COPD with its individual components, tiotropium monotherapy and placebo. Anoro Ellipta® 62.5/25 micrograms improved trough FEV1 by 0.090 litres (90ml) compared with both vilanterol alone and tiotropium 18 micrograms over 24 weeks (n=846). Improvements of trough FEV1 of 0.112 litres (112ml) was also observed with Anoro Ellipta® 62.5/25 micrograms compared with tiotropium 18 micrograms in another trial over 24 weeks (n=905). Improvements of trough FEV1 of 0.052 litres (52ml) were observed with Anoro Ellipta® 62.5/25 micrograms compared with umeclidinium 62.5 micrograms

and 0.095 litres (90ml) compared with vilanterol 25 micrograms over 24 weeks (1 RCT; n=1532; 24 weeks). However, the clinical significance of this difference is unclear as the full NICE guideline on COPD considers 0.100 litres (100ml) to be the minimum clinically important difference for change in FEV1.[60] Of note, however is that the European Public Assessment Report for Anoro Ellipta® states that a minimum clinically important difference of 0.100 litres is for comparisons with placebo and it may not be appropriate for comparisons between a combination of two bronchodilators (LAMA plus LABA) with one bronchodilator (either a LAMA or a LABA).[69]

- There is limited evidence on patient-orientated outcomes such as shortness of breath, quality of life outcomes or exacerbation rates. There was a statistically significant improvement in transition dyspnoea index (TDI) score with Anoro Ellipta® compared with placebo of 1.2 units. No statistically significant difference in TDI score was seen compared with umeclidinium or vilanterol monotherapy (1 RCT; n=1532; 24 weeks).[60]
- The overall safety profile was in line with the safety profile of other LAMAs and LABAs. However, the European assessment report did highlight that long term safety data is limited.[69] A long term 52-week safety study has been published using a 125/25 micrograms and does not include the licensed Anoro Ellipta® dose.[70]
- Whilst Anoro Ellipta® has been compared with its individual components and tiotropium, there are no published studies that compare Anoro Ellipta® with currently available LAMA and LABA treatment given concomitantly.

Aclidinium/formoterol 340/12 (Duaklir Genuair®)

- Duaklir Genuair® was launched in December 2014. This is also a multi-dose dry powder combination containing a LABA and a LAMA delivered via the Genuair® device.
- The clinical efficacy of the fixed-dose Duaklir Genuair® combination has been evaluated in two 24-week, double-blind, phase III studies (AUGMENT COPD and ACLIFORM COPD) involving approximately 4,000 patients with COPD. In the AUGMENT COPD study, Duaklir Genuair® improved lung function (as defined by improvement from baseline in 1-hour post-dose FEV1) at week 24 compared with aclidinium monotherapy (108ml; $p<0.0001$). Improvements in trough FEV1 were also significantly greater in patients treated with Duaklir Genuair® versus formoterol monotherapy (45ml; $p=0.0102$). Dual therapy with Duaklir Genuair® also produced a significant improvement from baseline in 1-hour post-dose FEV1 compared to aclidinium monotherapy in the ACLIFORM study (+125ml, $p<0.001$). Duaklir Genuair® significantly improved trough FEV1 over formoterol monotherapy by 85ml ($p<0.001$).[62]
- At week 24 in the ACLIFORM and AUGMENT studies, a significant improvement in transient dyspnoea index (TDI) focal score was observed with Duaklir Genuair® fixed-dose compared with placebo (1.29 units; $p<0.001$ and 1.44 units, $p< 0.0001$ respectively).[62]
- Duaklir Genuair® demonstrated statistically significant improvements in TDI score vs. separate aclidinium and formoterol monocomponents (0.44 ($p<0.05$) and 0.47 ($p<0.01$) points respectively) in a pre-specified pooled analysis of the AUGMENT and ACLIFORM studies. However, the treatment differences of less than half a unit are below the minimum 1 unit improvement in TDI score, which is generally considered to be clinically relevant.
- In both studies, more than 50% of patients administered Duaklir Genuair® achieved the minimum clinically important difference (4.35 units, $p<0.0001$) in SGRQ at week 24.[62]
- In a pre-specified pooled analysis, Duaklir Genuair® reduced the rate of moderate and severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; $p=0.036$) by 29% compared with placebo. A statistically significant difference was seen in the rate of exacerbations of any severity using the EXAcerbations of Chronic pulmonary disease Tool (EXACT) definition (1.18 per

patient/year vs. 1.51 per patient/year with placebo, p=0.01). Comparisons between the combination and aclidinium and formoterol monotherapies are not reported.[62]

- The safety experience with Duaklir Genuair® comprised exposure at the recommended therapeutic dose for up to 12 months. Adverse reactions associated with Duaklir Genuair® were similar to those of the individual components.[62]

Tiotropium/olodaterol 2.5/2.5 (Spiolto Respimat®)

- Spiolto Respimat® is a multi-dose LABA + LAMA combination delivered via the Respimat® inhaler. Administration is two puffs daily delivering 5mcg tioptropium and 5mcg olodaterol.
- In two multi-centre 52 week RCTs (TONADO 1 & 2), Spiolto Respimat® improved lung function compared with the monotherapy components:
  - FEV1 AUC0-3: treatment difference of 0.123L (123ml) vs. olodaterol 5mcg and 0.117L (117ml) vs. tiotropium 5mcg in TONADO 1; 0.132L (132ml) vs. olodaterol 5mcg and 0.103L (103ml) vs. tiotropium 5mcg in TONADO 2 (all p<0.0001).
  - Trough FEV1: 0.082L (82ml) vs. olodaterol 5mcg and 0.071L (71ml) vs. tiotropium 5mcg in TONADO 1 (both p<0.0001); 0.088L (88ml) vs. olodaterol 5mcg and 0.050L (50ml) vs. tiotropium 5mcg in TONADO 2 (p<0.0001 and p=0.0001 respectively).[24,71]
- After 24 weeks there was a statistically significant improvement in mean SGRQ total score compared to tiotropium and olodaterol (treatment difference of -1.693 vs. olodaterol 5mcg and -1.233 vs. tiotropium 5mcg (p<0.0001 and p=0.0001 respectively)).[24,71]
- More patients treated with Spiolto Respimat® showed a greater mean difference improvement in TDI (MCID defined as a value of at least 1 unit) compared with those who used tiotropium or olodaterol alone (54.9% vs. 50.6% [p=0.0546] or 54.9% 48.2% [p=0.0026]).[24]
- Spiolto Respimat® appears to have a similar safety profile to that of the monotherapy components.[24]
- Spiolto Respimat® should be used with caution in patients with moderate to severe renal impairment (CrCl≤50ml/min). There is no long term experience in patients with severe renal impairment.[24]

ICS/LABA inhalers

The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial and their role in management of stable COPD is limited to specific indications. Regular ICS improve symptoms, lung function and quality of life and reduce the frequency of exacerbations in COPD patients with an FEV1 <60% predicted.[2] There is no good evidence that ICS improve survival in patients with COPD, or reduce the rate of FEV1 decline.

NICE guidelines for COPD recommend considering an ICS/LABA combination in people with:[1]

- Stable COPD with FEV1 <50% who remain breathless or have exacerbations despite using short acting bronchodilators as required or
- Stable COPD and an FEV1 ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA or a LAMA or
- In addition to a LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV1.[1]

The GOLD guidelines also recommend ICS/LABA combinations in patients with severe (30% ≤FEV1, <50% predicted) and very severe (<30% FEV1 predicted) airflow limitation and for patients with frequent exacerbations not adequately controlled by long acting bronchodilators.[2]

There are now five ICS/LABA combination products licensed for use in COPD:

- Fluticasone propionate/salmeterol, Seretide® 500 Accuhaler® (one puff twice a day).
- Budesonide/formoterol, Symbicort® 200 Turbohaler® (two puffs twice a day) and Symbicort® 400 Turbohaler® (one puff twice a day).

- Budesonide/formoterol, DuoResp® Spiromax®160/4.5 (two puffs twice daily) and DuoResp® Spiromax® 320/9 (one puff twice daily).
- Fluticasone furoate/vilanterol, Relvar® Ellipta® 92/22 (one puff daily).
- Beclometasone dipropionate/formoterol, Fostair® 100/6 inhaler (two puffs twice daily).

It is important to ensure these products are prescribed at the correct licensed dose for COPD.

Although not all ICS/LABA combination inhalers are licensed for the treatment of COPD, audit suggests that the MDI inhalers are often used off licence in COPD patients, particularly where patients are unable to use the breath actuated devices. If these products are used in COPD, they should be used with a spacer device to ensure the appropriate dose is being administered and minimise side effects. Fostair® is currently the only MDI with a marketing authorisation for the treatment of COPD.

Withdrawal from treatment with ICS may lead to exacerbations in some patients. If this is being considered, patients should be counselled to increase use of when required SABA such as salbutamol, and be prescribed rescue medication such as a course of steroids and antibiotics for exacerbations. Regular treatment with ICS does not modify the long term decline of FEV1, nor mortality in patients with COPD.

Evidence on the three newer products is provided below.

Beclometasone/Formoterol 100/6 (Fostair®)

- In April 2014, a license extension was granted for the use of Fostair® in people with COPD (FEV1<50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long acting bronchodilators. It is the only MDI licensed for COPD.
- In a randomised controlled trial (RCT; n=718), Fostair® was non-inferior to Symbicort® in improving pre-dose morning lung function in people with severe COPD over 48 weeks. There was no significant difference between the treatments in the rate of COPD exacerbations/patient per year. The incidence of adverse events was similar between the treatments. This study also included a formoterol alone arm.[72]
- In a second RCT (n=419), Fostair® statistically significantly improved the onset of bronchodilation (FEV1 0-30mins) in people with moderate-to-severe COPD compared with Seretide®, although it is unclear whether the improvement is clinically important. The treatments were equivalent in improving dyspnoea over 12 weeks. Serious adverse events were statistically significantly more common with Seretide®.[72]
- From the published data, Fostair® appears to work as well in COPD as the two commonly used ICS/LABA combinations, its constituent ingredients have been available for many years so their safety profile is known, it costs less than most alternatives and it can be used with a spacer, which many people with COPD need.[72]
- Fostair® was accepted for by the SMC for the symptomatic treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. Fostair® should be used in patients for whom beclometasone and formoterol are appropriate choices of corticosteroid and long acting $beta_2$ agonist respectively, and for whom a metered dose inhaler is an appropriate delivery device.[73]

Budesonide/Formoterol (DuoResp®)

- DuoResp® is a new dry powder inhaler containing budesonide and formoterol which has been granted an EU licence as a hybrid medicinal product using Symbicort® as a reference product.
- This is a direct competitor for Symbicort®. The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively.

- In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with severe COPD was evaluated. Median FEV1 at inclusion in the trials was 36% of predicted normal. The mean number of exacerbations per year (as defined above) was significantly reduced with DuoResp® as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the DuoResp® group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV1, DuoResp® was not superior to treatment with formoterol alone.[27] The SPC also documented that COPD patients were able to achieve the inspiratory flow rates through the Spiromax® device that were similar to Symbicort Turbohaler®.
- It is imperative that DuoResp® preparations are prescribed by brand to ensure that a consistent product is supplied and that patients are trained in the correct inhaler technique.

Fluticasone furoate/vilanterol (Relvar®)

- Relvar® contains a once daily combination of fluticasone furoate (ICS) and vilanterol (LABA). This is delivered through a multi-dose dry powder inhalation Ellipta® device.
- Only the 92/22 strength is licensed in COPD at a dose of 1 puff daily.
- The NICE evidence summary analysed two randomised, double-blind, parallel group studies (total n=3255). In a 12 week study comparing Relvar® 92/22 (n=266) with Seretide® 500/50 (n=262), Relvar® was not shown to be superior in improvement from baseline in 0-24 hour weighted mean FEV1; although a clinically meaningful improvement was observed with both Relvar® (mean ± SD = 130 ± 222 mL) and Seretide® (mean ± SD =108 ± 221 mL). The NICE guideline on COPD considers a 100ml change to be a clinically important difference in FEV1. The second study showed that Relvar® improved trough FEV1 after 24 weeks treatment compared with placebo but not compared to vilanterol alone. Local corticosteroid effects, pneumonia (including requiring admission to hospital) and non- traumatic fractures were seen more frequently with Relvar® than with vilanterol alone.[74]
- Relvar® reduced the mean yearly rate of moderate and severe exacerbations compared with vilanterol alone from 1.11 to 0.81. However, there was no statistically significant difference in the mean yearly rate of exacerbations requiring admission to hospital compared with vilanterol 25 micrograms on its own. The comparator vilanterol is not an established monotherapy treatment licensed for use.[74]
- In terms of secondary outcomes (QoL) measured by the SGRQ for COPD, total score improved from baseline for both Relvar® (-4.3 units) and Seretide (-3.0 units), although the difference between scores was not statistically significant. Exacerbations occurred in 2-3% of patients in the comparative trial and 7-9% of fluticasone furoate/vilanterol-treated patients in the placebo-controlled trials (10% with placebo).[75]
- There are no published studies comparing efficacy, safety and frequency of exacerbations of Relvar® with other ICS/LABA combination inhalers (other than Seretide) licensed for use in COPD.
- There is no long term efficacy and safety data beyond one year. Further long term data on pneumonia and fractures is needed.
- MTRAC considered that the evidence for Relvar® was relatively weak.[76]
- Concern has also been raised that the device is contained within a sealed foiled pouch and once opened, the shelf life is six weeks, which may increase the risk of patients using an expired inhaler. The colour of Relvar® has now been changed from blue to yellow as a result of concerns associated with the similarity of a blue inhaler colour to a reliever inhaler and the possibility of accidental steroid overdose.

Safety of ICS

Care needs to be taken when prescribing an ICS/LABA in COPD as prolonged treatment with inhaled corticosteroids at high doses carries a risk of systemic side effects and can induce adrenal suppression or crisis, glaucoma and cataracts and a range of psychological and behavioural effects such as psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression. In COPD patients in particular, there is also an increased risk of fractures and pneumonia with high dose inhaled corticosteroid use.

A large Cochrane systematic review of 43 randomised controlled trials provides evidence that taking fluticasone or budesonide alone or in combination with a LABA increases the risk of non-fatal serious pneumonia events (requiring hospital admission) in people with COPD. No increase in total mortality was found. Studies ranged from three months to 36 months and the studies for budesonide were shorter than that for fluticasone. When comparing risk with budesonide and fluticasone, no statistical difference in serious pneumonias, mortality or serious adverse events was seen between the two ICS. However, the risk of any pneumonia (i.e. less serious cases dealt with in the community) was higher with fluticasone than with budesonide. The authors acknowledge that definitions and methods of diagnosis used in studies are a potential confounding factor in their comparison and that therefore this finding should be interpreted with caution.[77] This systematic review supports earlier RCTs.[78]

A recent observational retrospective matched cohort study published in the BMJ found that patients with COPD who were treated with Seretide® were significantly more likely to experience pneumonia and had a higher mortality related to pneumonia than patients treated with Symbicort®; the rate of diagnosis of pneumonia per 100 patient years was 11.0 in the Seretide® cohort and 6.4 in the Symbicort® cohort ($p<0.001$). The higher risk of pneumonia with Seretide® was independent of whether or not patients had a recorded episode of pneumonia before the index date. Findings showed no dose-response relationship with regard to increased risk of pneumonia with the two treatments—that is, any excess risk was linked with the choice of ICS/LABA and not the dose prescribed and collected by the patient. These results have to be demonstrated in independent studies.[79]

The European Medicines Agency (EMA) has taken the decision to review ICS containing medication to evaluate the risk of pneumonia in patients with COPD, i.e. this will form part of the risk-management plan for Relvar® and the applicant will conduct two post-authorisation safety studies to further investigate this risk.[80]

MHRA advice is to be vigilant for the development of pneumonia and other infections of the lower respiratory tract when using ICS to treat people with COPD, and supports the approach set out in NICE guidance for the care of people with COPD.[81] NICE states: "*Be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss with patients.*"[1]

ICS have also been associated with a dose-related increase of both diabetes onset and progression. A Canadian cohort study identified that patients treated for respiratory disease using ICS over a period of 5.5 years were, on average, at a 34% increased risk of both diabetes onset and diabetes progression compared with patients not treated with ICS. The risk increased with increasing dose of ICS. Patients treated with high doses of ICS, equivalent to fluticasone 1000microgram/day or more, had, on average, a 64% increased risk of developing diabetes compared with patients not treated with ICS. This study is limited by its observational nature: the analysis was subject to the influence of many confounders, and not all of them (e.g. obesity) were able to be taken into account. However, the association is strengthened by the dose relationship shown between ICS dose and risk of diabetes.[82]

Bone mineral density may be reduced following long term inhalation of higher dose corticosteroids, predisposing patients to osteoporosis.

As there is more emerging evidence of the harms associated with use of long term inhaled steroids in COPD, continued prescribing should be reviewed regularly and discontinued if exacerbations are not reduced. It is important to review the use of high dose ICS in COPD patients with co-morbidities such as diabetes, osteoporosis and psychological problems and assess the risk verses the benefit of continuing with treatment.

Any plans to discontinue ICS therapy should be discussed with the local respiratory consultant to ensure they are on board with the proposed changes.

As a result of the risk of systemic side effects, patients who require prolonged high dose ICS should be issued with a steroid treatment card. See PrescQIPP respiratory webkit for further information: http://www.prescqipp.info/respiratory#london-respiratory-network-high-dose-inhaled-corticosteroid-card

Stepping down ICS therapy in mild to moderate COPD with infrequent or no exacerbations

In patients with milder disease and infrequent/no exacerbations, the role of triple therapy has not been established. Rather, maximal achievable bronchodilation should be the strategy for this patient group, supported by exercise and pulmonary rehabilitation, as this improves dynamic lung function, aiding daily activity and enhancing quality of life.[1]

Of note, is that the rate at which exacerbations occur varies greatly between patients. The best predictor of having frequent exacerbations (two or more exacerbations per year) is a history of previous treated events. In addition, worsening airflow limitation is associated with an increasing prevalence of exacerbations and risk of death. Hospitalisation for a COPD exacerbation is associated with a poor prognosis with increased risk of death.[2]

For patients with FEV1>50% and no history of asthma and no history of exacerbations, it may be possible to reduce ICS combination therapy slowly over three months. There is limited evidence on dose reduction of ICS in COPD. Withdrawal from treatment with ICS may lead to exacerbations in some patients, although in a study with severe and very severe COPD patients, ICS could be gradually withdrawn over a three month period without increasing the medium risk of exacerbations, although lung function deteriorated significantly.[7,83,84]

A virtual clinic approach has been reported which reviewed high dose ICS as appropriate, resulting in a 4% decrease in prescribing (as a proportion of total ICS use).[85] Guidance on this is provided in attachments 3a (flow chart), 3b (Reducing regime, based on the Lambeth reducing regimen), 3c (patient letter) and 3d (audit tool). As mentioned above, any plans to review and discontinue ICS therapy should be discussed with the local respiratory consultant and involve a multidisciplinary approach to carefully identify exacerbation risk and ensure regular review of patient when stepping down.

Patients with a previous history of asthma

Occasionally patients will have a diagnosis of both asthma and COPD. This can happen in particular in patients who are aged 40 and over, are smokers that have had a previous history of asthma and their disease is now becoming irreversible.

Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Prevalence is stated as being between 15% and 55%, depending on the inclusion criteria used. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15% and 20% of patients. GOLD has produced assessment tools to enable clearer diagnosis that compares the number of features in favour of a diagnosis of asthma or COPD.

Faced with a differential diagnosis equally balanced between asthma and COPD (i.e. ACOS) the default position should be to start treatment accordingly for asthma. This recognises the pivotal role of ICS in preventing morbidity and even death in patients with uncontrolled asthma symptoms, for whom even seemingly 'mild' symptoms (compared to those of moderate or severe COPD) might indicate significant risk of a life-threatening attack.

If assessment suggests asthma or ACOS, or there is significant uncertainty about the diagnosis of COPD, it is prudent to start treatment as for asthma until further investigation has been performed to confirm or refute this initial position. Treatments will include an ICS (in a low or moderate dose, depending on

level of symptoms). A LABA should also be continued (if already prescribed), or added (but not as LABA monotherapy).

If the assessment suggests COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be commenced, but not ICS alone (as monotherapy).[86]

At this stage it may be possible to step down the asthma treatment in line with British Thoracic Society (BTS) guidelines (particularly if they are using a high dose ICS/LABA combination inhaler). It would also seem sensible to initiate treatment with a LAMA if they are having exacerbations on an ICS/LABA combination as the LABA alone may be ineffective. These patients may benefit from increased use of their SABA whilst their ICS/LABA is being stepped down and may also need to have rescue medicines prescribed. They will need to be closely monitored. If the asthma treatment is not stepped down the patient could end up on triple therapy at the start of their treatment, which is not cost effective.

Management of exacerbations

Out of the estimated three million patients in the UK with COPD, 83% report frequent exacerbations and many of these wait five to six days before taking action. COPD exacerbations account for 10% of all medical admissions and have the highest 30 day re-admission rate.[79] Frequent exacerbations of COPD cause further lung function decline and increase morbidity and mortality. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE) study showed that although COPD exacerbations were increasingly seen as the patient's disease worsened, the strongest predictor of future exacerbations was a previous history of exacerbation. This was observed across all patients, regardless of their disease severity. In those who did not exacerbate, the risk of exacerbating in the future was significantly less.[87]

The ECLIPSE study confirms the growing realisation that COPD is a heterogeneous disease – in other words, it behaves in different ways in different people. This view that COPD sub-groups, or phenotypes exist which has led to a developing interest in matching treatments to type. The evidence for using combinations in people with two or more exacerbations recognises that those who exacerbate are more likely to continue to exacerbate without treatment with a combination inhaler, whereas those whose phenotype is breathlessness will arguably be better served with bronchodilator therapy, a LAMA, LABA or both.

The direct cost to the NHS of treating COPD exacerbations is £800 million per year. COPD exacerbations are associated with increased mortality, and faster disease progression, this can often result in emergency hospital admission and subsequent re-admissions. Ensuring that patients are aware of the signs and symptoms of an exacerbation and can manage these in a timely manner will result in less lung damage, faster recovery and fewer admissions and re-admissions to hospital releasing significant savings for the NHS. Prescribing rescue packs of antibiotics and steroid treatment supported by an education and self-management plan is a cost-effective intervention.[88,89]

Patients at risk of having an exacerbation of COPD should be encouraged to respond quickly to the symptoms of exacerbation by:

- Starting oral corticosteroid therapy (unless contra-indicated) if increased breathlessness interferes with activities of daily living.
- Starting antibiotic therapy if their sputum is purulent.
- Adjusting bronchodilator therapy to control symptoms.

Patients at risk of exacerbations should be prescribed a course of antibiotics and corticosteroid tablets to keep at home as rescue medication. The use of these treatments should be monitored and patients advised to contact a named healthcare professional if symptoms do not improve. The patient information leaflets in attachments 4 and 5 will support organisations wanting to implement self management plans and prescribing of rescue packs for COPD patients.

Savings

Current spend

Annual spend across England (ePACT March - May 2015) for commonly prescribed COPD treatments is approximately:

- £193.7 million on LAMA drugs
- £30.6 million on LABA drugs
- £1.2 million on the LABA/LAMA combination tratments.

£296.9 million on ICS/LABA licenced for the treatment of COPD. In addition there is a £155.1 million spend on Seretide® 250 Evohaler® which is not licenced for COPD but often used.

- It is assumed that approximately 50% of the ICS/LABA prescribing is for COPD although not all ICS/LABA combination products are licenced for use in COPD.
- Current annual spend on LABAs across England is £30.6 million. **A switch to formoterol Easyhaler could result in potential annual savings of £15.7 million annually across England or £27,657 per 100,000 patients.**
- Current annual spend on LAMAs across England is £193.7 million. Whilst there is no current evidence to support a switch from tiotropium to the newer LAMAs, they could be used in new patients dependent on the delivery device that was most suitable for the patient.
- Current spend on Seretide® 250 Evohaler® is £155.1 million. Assuming that 50% prescribing is for COPD and a MDI is suitable, **a switch to Fostair® could result in potential annual savings across England of £31.2 million or £54,818 per 100,000 patients.**
- Current annual spend on Symbicort® Turbohaler® or Seretide® 500 Accuhalers® is £238.1 million. A switch to cost effective dry powder inhalers, DuoResp® Spiromax® or Relvar® Ellipta® 92/22 respectively **could result in potential annual savings of £59.4 million across England or £104,024 per 100,000 patients.**
- If an ICS is not appropriate in COPD with mild to moderate severity, **a 10% reduction in ICS could result in annual savings of £22.6 million.** Slow ICS reduction in dosage with follow up is needed (attachments 3a-d).

It is important to ensure that patients who are switched are trained on correct inhaler technique and are followed up.

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Additional PrescQIPP resources

 **Briefing**

 **Data pack**

 **Implementation resoures**

Available at: http://www.prescqipp.info/inhaled-therapy-in-copd/viewcategory/191

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