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Drug Class Literature Scan: Anticholinergics, Inhaled

Date of Review: Oct 2021

Date of Last Review: Oct 2020
Literature Search: 07/08/20 – 08/12/21

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Guidelines from the National Asthma Education and Prevention Coordinating Committee Expert Panel Working Group (NAEPPCC) included recommendations related to the use of long acting muscarinic antagonists (LAMAs)[1,2]:
  - In individuals aged 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends against adding LAMA to inhaled corticosteroids (ICS) compared to adding long-acting beta-2 agonists (LABA) to ICS (Conditional recommendation; Moderate certainty of evidence)
  - If LABA is not used, in individuals aged 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS controller therapy compared to continuing the same dose of ICS alone. (Conditional recommendation; Moderate certainty of evidence)
  - In individuals aged 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA. (Conditional recommendation; Moderate certainty of evidence)
  - Patients with glaucoma and urinary retention should not receive LAMA therapy, and the risks of LAMA may outweigh benefits in other populations, including Blacks.
- One comparative study, a pre-specified pooled analysis of 2 comparative trials, showed non-inferiority of fluticasone furorate/umeclidinium/vilanterol 100/62.5/25 mcg once daily versus budesonide/formoterol 400/12 mcg twice daily + tiotropium 18 mcg once daily in chronic obstructive pulmonary disease (COPD) patients for the primary outcome of mean change from baseline in forced expiratory volume in 1 second (FEV_1) over 0 to 24 hours at week 12 (mean change 14 mL, 95% confidence interval [CI] -5 mL to 34 mL, non-inferiority margin 50 mL). Adverse reactions were similar between groups.

Recommendations:

- New clinical evidence did not warrant changes to the preferred drug list (PDL).
- After executive session, Combivent® Respimat® and Incruse® Ellipta® were made preferred.

Summary of Prior Reviews and Current Policy

- Evidence for asthma and chronic obstructive pulmonary disease (COPD) maintenance medications were reviewed in October 2020. Current preferred drug list included in **Appendix 1**.
- All non-preferred LABA, ICS, LABA/ICS, and LAMA/LABA inhalers require PA to ensure appropriate step therapy.

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- New clinical evidence did not warrant changes to the preferred drug list (PDL).
- After executive session Tudorza was made non-preferred and the following were made preferred; Anoro Ellipta and Stiolto Respimat.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
After review, 14 systematic reviews were excluded due to poor quality, [3-11] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[12-14] retracted,[15] or outcome studied (e.g., non-clinical).[16]

New Guidelines:
High Quality Guidelines:

<u>NAEPPCC-2020 Focused Updates to the Asthma Management Guidelines</u>[1,2]
This guideline utilized systematic reviews on relevant topics which were conducted by the AHRQs Evidence-Based Practice Centers and published between October 2017 and March 2018. Westat, a hired contractor, conducted literature searches to identify new publications between the completion of the AHRQs search and October 2018, when the Panel began work. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methods were used for certainty of evidence, as well as direction and strength of recommendations. Conflicts of interest (COI) within the Panel were well delineated and, when applicable, individual panel members were appropriately recused from various activities (drafting, discussing, voting, etc). The *critical* outcomes assessed for recommendations across all topic areas were asthma exacerbations, asthma control, and asthma-related quality of life (QoL). The panel considered other *important* outcomes (e.g., asthma symptoms) when these critical outcomes were not relevant or available for the key question. The update focused on six priority topics as determined by needs assessment and stakeholder input, one topic being LAMAs in asthma management as add-ons to inhaled ICSs. The key questions for this topic were:

1. What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in individuals aged 12 years and older with uncontrolled, persistent asthma?
2. What is the comparative effectiveness of LAMA as add-on to ICS controller therapy compared to placebo or increased ICS dose in individuals aged 12 years and older with uncontrolled, persistent asthma?

3. What is the comparative effectiveness of LAMA as add-on to ICS-LABA compared to ICS-LABA as controller therapy in individuals aged 12 years and older with uncontrolled, persistent asthma?

Recommendations for the key questions based on analysis of the data are presented in **Table 1**. The panel did not review data for patients aged 6 to 11 years. All studies reviewed tiotropium, the only drug with a Food and Drug Administration (FDA) indication for asthma at the time, with the exception of one study including umeclidinium. Additional considerations from the panel related to LAMA therapy include:

- LAMA can be used as an add-on to ICS therapy in individuals aged 12 years and older with uncontrolled asthma therapy as part of Step 4 therapy, but add-on LABA therapy has a more favorable benefit-harm profile.
- Individuals at risk of urinary retention or with glaucoma should not receive LAMA therapy.
- The small increase in the potential risk of harms from a LAMA may outweigh its benefits in some individuals, particularly in Blacks.
- LAMA treatment requires appropriate use of specific inhaler devices and individuals should be taught how to use these devices appropriately.
- LAMA therapy should be initiated for long-term asthma control in the ambulatory setting and does not have a role in the management of acute exacerbations of asthma in the ambulatory, emergency department, or inpatient settings.
- Diagnosis should be confirmed and mitigating factors addressed for uncontrolled asthma before intensification of therapy.

Table 1. Expert Panel Recommendations for Key Questions[1,2]

Intervention	Comparator	Recommendation	Certainty of Evidence
LAMA as an add-on to ICS controller therapy	LABA as an add-on to same-dose ICS controller therapy	Conditional Against intervention	Moderate
	Montelukast as an add-on to same-dose ICS controller therapy	No recommendation	Insufficient
LAMA as an add-on to ICS controller therapy	Same-dose ICS controller therapy + placebo	Conditional In favor of the intervention	Moderate
	Increased ICS dose	No recommendation	Insufficient
LAMA as an add-on to ICS-LABA	Same-dose ICS-LABA as controller therapy	Conditional In favor of the intervention	Moderate
	Doubled ICS dose + LABA	No recommendation	Insufficient

Additional guidelines for Clinical Context:

GINA – Global Strategy for Asthma Management and Prevention[17]

GINA updates their recommendations on an annual basis to guide diagnosis and management of asthma in adults and adolescents. Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D, with A level evidence defined as: well-designed randomized controlled trials, meta-analyses or post-hoc or observational data. There is no risk of bias assessment used as inclusion criteria for publications used for guideline development. Other limitations to the guideline include the absence of the following: target users, objective of the guidelines, specifics on evidence selection, diversity in representation from professional groups, patient and public input, external review by experts in the

field, and discussion on resource implications/barriers of recommendations. Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.

Specific recommendations for therapy at each step for asthma were extensively covered in the October 2020 class update.[18] New 2021 recommendations include the following minor updates:

- Recommendations for adding tiotropium to ICS/LABA have been expanded to include triple therapy combinations of ICS/LABA/LAMA in patients ≥18 years in step 5. This is based on evidence of modest improvement in lung function (though no change in symptoms) and small reduction in exacerbations in some studies.
- Recommendations for adding LAMA as a non-preferred "other" option in step 4. Patients with exacerbations should receive at least medium dose ICS/LABA before consideration of a LAMA.

GOLD – Global Initiative for Chronic Obstructive Lung Disease[19]

A 2021 update on the management of COPD was published by GOLD. Methodology is the same as for the GINA guidelines (above) with the associated limitations as well. Specific recommendations for therapy were extensively covered in the October 2020 class update.[18]

Updates to the section on triple therapy (ICS/LABA/LAMA) were made to incorporate data from the post-hoc pooled analysis of the IMPACT and ETHOS trials on mortality in symptomatic patients with frequent and/or severe exacerbations. This was a pre-specified, non-primary outcome. Both studies found triple therapy reduced mortality compared to LABA/LAMA (only for triple therapy with high dose, not low dose, ICS in ETHOS), but was no different to the LABA/ICS arm.

New Formulations:

None

New FDA Safety Alerts:

None

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Glycopyrrolate	SEEBRI	July 2021	Warnings	"including Anaphylaxis" added to Hypersensitivity Reactions
Glycopyrrolate; Indacterol Maleate	UTIBRON	July 2021	Warnings	"including Anaphylaxis" added to Hypersensitivity Reactions

References:

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4. Ferguson GT, Darken P, Ballal S, et al. Efficacy of Budesonide/Glycopyrronium/Formoterol Fumarate Metered Dose Inhaler (BGF MDI) Versus Other Inhaled Corticosteroid/Long-Acting Muscarinic Antagonist/Long-Acting beta₂-Agonist (ICS/LAMA/LABA) Triple Combinations in COPD: A Systematic Literature Review and Network Meta-analysis. *Advances in Therapy.* 2020;37(6):2956-2975.
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12. Buhl R, de la Hoz A, Xue W, Singh D, Ferguson GT. Efficacy of Tiotropium/Olodaterol Compared with Tiotropium as a First-Line Maintenance Treatment in Patients with COPD Who Are Naive to LAMA, LABA and ICS: Pooled Analysis of Four Clinical Trials. *Advances in Therapy.* 2020;37(10):4175-4189.
13. Xu H, Tong L, Gao P, et al. Combination of ipratropium bromide and salbutamol in children and adolescents with asthma: A meta-analysis. *PLoS ONE [Electronic Resource]*. 2021;16(2):e0237620.
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20. Ferguson GT, Brown N, Compton C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. *Respir Res.* 2020;21(1):131.

Appendix 1: Current Preferred Drug List

Inhaled Anticholinergics Class

Generic	Brand	Route	Form	PDL
ipratropium bromide	ATROVENT HFA	INHALATION	HFA AER AD	Y
ipratropium bromide	IPRATROPIUM BROMIDE	INHALATION	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	INHALATION	AMPUL-NEB	Y
tiotropium bromide	SPIRIVA	INHALATION	CAP W/DEV	Y
aclidinium bromide	TUDORZA PRESSAIR	INHALATION	AER POW BA	N
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	INHALATION	VIAL-NEB	N
glycopyrrolate	SEEBRI NEOHALER	INHALATION	CAP W/DEV	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	INHALATION	VIAL-NEB	N
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	INHALATION	MIST INHAL	N
revefenacin	YUPELRI	INHALATION	VIAL-NEB	N
tiotropium bromide	SPIRIVA RESPIMAT	INHALATION	MIST INHAL	N
umeclidinium bromide	INCRUSE ELLIPTA	INHALATION	BLST W/DEV	N

LAMA/LABA Combinations Class

Generic	Brand	Route	Form	PDL
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	INHALATION	MIST INHAL	Y
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	INHALATION	BLST W/DEV	Y
aclidinium brom/formoterol fum	DUAKLIR PRESSAIR	INHALATION	AER POW BA	N
budesonide/glycopyr/formoterol	BREZTRI AEROSPHERE	INHALATION	HFA AER AD	N
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	INHALATION	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	INHALATION	HFA AER AD	N

Appendix 2: New Comparative Clinical Trials

A total of 68 citations were manually reviewed from the initial literature search. After further review, 67 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Ferguson et al.[20] NCT03478683 N=690 NCT03478696 N=700 RCT, DB, TD, MC, non-inferiority, mPP, ITT, prespecified pooled analysis of 2 studies, MMRM	1. FF/UMEC/VI 100/62.5/25 mcg once daily 2. BUD/FOR 400/12 mcg twice daily + TIO 18 mcg once daily 4 week run-in and received group 2 treatment prior to 1:1 randomization to a treatment for 12 weeks.	-outpatients ≥ 40 years -current or former smoker ≥ 10 pack-years -established COPD -maintenance therapy ≥ 3 months -FEV_1 < 50% predicted or (post-bronchodilator FEV_1 < 80% predicted & ≥ 2 moderate or 1 severe exacerbation in past 12 months) -post-bronchodilator FEV_1/FVC ratio <0.70 -CAT score ≥ 10 -excluded asthma or other respiratory d/o	Weighted mean change from baseline in FEV_1 over 0-24 h at week 12 Non-inferiority margin 50 mL	Study 1; 1 vs 2, mPP 15 mL, 95% CI -13 to 43 mL Study 2; 1 vs 2, mPP 11 mL, 95% CI -20 to 41 mL Pooled analysis; 1 vs 2, ITT 14 mL, 95% CI -5 to 34 AE leading to withdrawal Study 1 1. 7 (2%) 2. 7 (2%) Study 2 1. 2 (<1%) 2. 5 (1%)

Abbreviations: ACQ-7 = asthma control questionnaire-7; AE = adverse event; BUD = budesonide; CAT = COPD assessment test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double blind; d/o = disorder; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FOR = formoterol; FVC = forced vital capacity; h = hours; ITT = intent-to-treat; MC = multicenter; MMRM = mixed model repeated measures analysis; mPP = modified per protocol; RCT = randomized clinical trial; SAL = salmeterol; TD = triple dummy; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

Appendix 3: Abstracts of Comparative Clinical Trials

Ferguson GT, Brown N, Compton C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. *Respir Res.* 2020;21(1):131.

BACKGROUND: The comparative efficacy of inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist (ICS/LAMA/LABA) triple therapy administered via single or multiple inhalers in patients with chronic obstructive pulmonary disease (COPD) has not been evaluated comprehensively. We conducted two replicate trials comparing single- with multiple-inhaler ICS/LAMA/LABA combination in COPD.
METHODS: 207608 and 207609 were Phase IV, 12-week, randomized, double-blind, triple-dummy non-inferiority trials comparing once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 mug via Ellipta inhaler, with twice-daily budesonide/formoterol (BUD/FOR) 400/12 mug via metered-dose inhaler plus once-daily tiotropium (TIO) 18 mug via HandiHaler. Patients had symptomatic COPD and forced expiratory volume in 1 s (FEV_1) < 50% predicted, or FEV_1 < 80% predicted and >= 2 moderate or 1 severe exacerbations in the prior year. The primary endpoint in both trials was weighted mean change from baseline (wmCFB) in 0-24-h FEV_1 at Week 12. Secondary endpoints included CFB in trough FEV_1 at Day 84 and 85. Other endpoints included serial FEV_1 and health status outcomes at Week 12. Safety was evaluated descriptively.
RESULTS: The modified per-protocol population included 720 and 711 patients in studies 207608 and 207609 (intent-to-treat population: 728 and 732). FF/UMEC/VI was non-inferior to BUD/FOR+TIO for wmCFB in 0-24-h FEV_1 at Week 12 (Study 207608 treatment difference [95% confidence interval]: 15 mL [- 13, 43]; Study 207609: 11 mL [- 20, 41]). FF/UMEC/VI improved trough FEV_1 CFB versus BUD/FOR+TIO at Day 84 and 85 (Day 85 treatment difference: Study 207608: 38 mL [10, 66]; Study 207609: 51 mL [21, 82]) and FEV_1 at 12 and 24 h post-morning dose at Week 12 in both studies. No treatment differences were seen in health status outcomes. Safety profiles were similar between treatments; pneumonia occurred in 7 (< 1%) patients with FF/UMEC/VI and 9 (1%) patients with BUD/FOR+TIO, across both studies.
CONCLUSIONS: FF/UMEC/VI was non-inferior to BUD/FOR+TIO for wmCFB in 0-24-h FEV₁ at Week 12 in patients with COPD. Greater improvements in trough and serial FEV_1 measurements at Week 12 with FF/UMEC/VI versus BUD/FOR+TIO, together with similar health status improvements and safety outcomes including the incidence of pneumonia, suggest that once-daily single-inhaler FF/UMEC/VI triple therapy is a viable option for patients looking to simplify their treatment regimen.
Trial registration: Gsk (207608/207609; nct03478683/nct03478696).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 12, 2021

# ▲	Searches	Results	Type	Actions	Annotations
1	Ipratropium/ or Albuterol, Ipratropium Drug Combination/	1893	Advanced	Display Results | More	
2	Tiotropium Bromide/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]	381	Advanced	Display Results | More	
3	aclidinium.mp.	236	Advanced	Display Results | More	
4	Glycopyrrolate/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]	769	Advanced	Display Results | More	
5	revefenacin.mp.	37	Advanced	Display Results | More	
6	umeclidinium.mp.	276	Advanced	Display Results | More	
7	1 or 2 or 3 or 4 or 5 or 6	3426	Advanced	Display Results | More	
8	limit 7 to (english language and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	1588	Advanced	Display Results | More	
9	limit 8 to yr="2020 -Current"	82	Advanced	Display Results | More	
10	Pulmonary Disease, Chronic Obstructive/dt, th [Drug Therapy, Therapy]	15734	Advanced	Display Results | More	
11	Asthma/de, dt, th [Drug Effects, Drug Therapy, Therapy]	52806	Advanced	Display Results | More	
12	10 or 11	66704	Advanced	Display Results | More	
13	8 and 9 and 12	74	Advanced	Display Results | More	
14	9 or 13	82	Advanced	Display Results | More	

Contract

Appendix 5: Key Inclusion Criteria

Population	Adults and children with asthma and adults with chronic obstructive pulmonary disease (COPD)
Intervention	Inhaled anticholinergic agents
Comparator	Comparator Inhaled anticholinergic agents
Outcomes	Mortality, exacerbations, hospitalizations
Timing	Not applicable
Setting	Outpatient

Appendix 6. Prior Authorization criteria

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist (LAMA/LABA) and LAMA/LABA/Inhaled Corticosteroid (LAMA/LABA/ICS) Combinations

Goals:

- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma and COPD: short-acting bronchodilator and previous trial of two drug combination therapy (ICS/LABA, LABA/LAMA or ICS/LAMA). Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA and LAMA/LABA/ICS products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #9	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a LAMA/LABA combination product?	**Yes:** Go to #7	**No:** Go to #8
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/21 (SF); 12/20 (KS), 10/20, 5/19; 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*