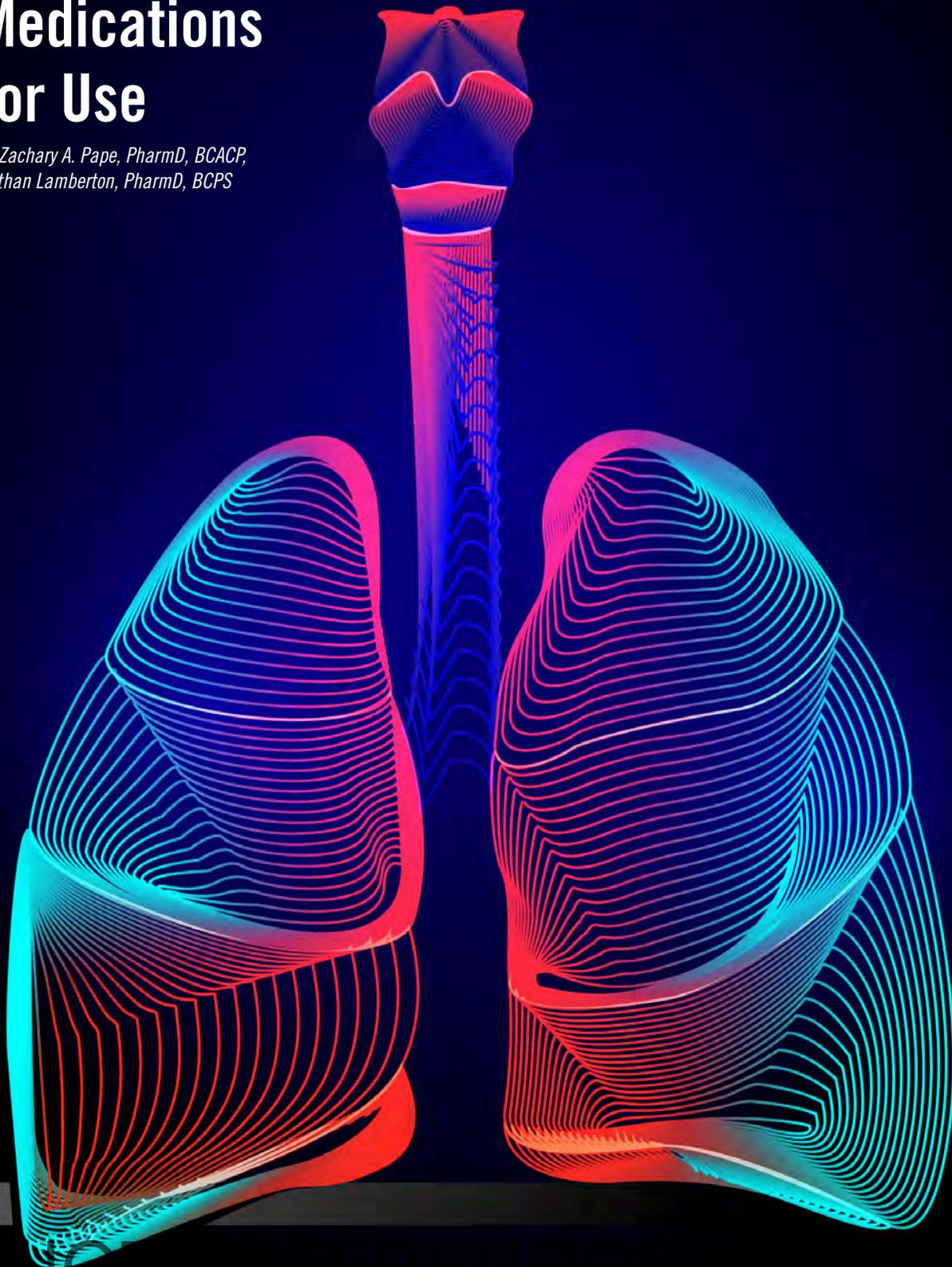


PHARMACIST CE:

An Overview of Recommended Asthma Treatments with New and Emerging Medications for Use

*by Zachary A. Pape, PharmD, BCACP,
Nathan Lamberton, PharmD, BCPS*



Asthma is a unique disease state that has the ability to plague an individual starting early in childhood and persisting through out their adult life. Characterized by chronic airway inflammation associated with reversible airflow obstruction and airway hyperresponsiveness, asthma results from the interplay between genetic and environmental factors.¹

Approximately 9.5% and 8.2% of US children and adults, respectively, have a diagnosis of asthma.² It accounts for over \$50 million US in health care costs per year and results in 14.2 million office and 1.8 million emergency department visits per year.²

Clinical Presentation

Asthma causes symptoms such as cough, shortness of breath (SOB), wheezing, and chest tightness, that are often relapsing and remitting in nature. Direct causes of these symptoms include airway narrowing, airway wall thickening, and increased mucus production. Typically, asthma is diagnosed based on two key factors: history of respiratory symptoms (e.g. cough, SOB, wheezing, chest tightness) and reversible airflow limitation (based on spirometry). Reversible airflow limitation is defined by a 1-second forced expiratory volume (FEV1) increase of more than 12% and 200mL after administration of a short-acting beta-agonist (SABA). Risk factors for developing asthma can be found in Table 1.³

To date, no interventions have shown a causal relationship in reducing the risk of developing of asthma. However, one

TABLE 1. Risk Factors for Developing Asthma²

Male gender
Parent with asthma
Parent smoking before child 1 year of age
Eczema at 4 years of age
Atopy at 4 years of age
Recurrent chest infections at 2 years of age
Antibiotic use before child 1 year of age

CE FOR PHARMACISTS

COMPLETE ARTICLE AND CE EXAM
AVAILABLE ONLINE: WWW.PSWI.ORG

Learning Objectives

- Define asthma and describe clinical features and presentation
- Review current recommendations regarding the assessment and management of asthma
- Identify medications and delivery devices that are used in the management of asthma
- Outline current therapeutic approach to the control and treatment of asthma
- Summarize potential use of newer therapeutic agents and their role(s) in therapy

Danish cohort study suggests that fish oil supplementation in the third trimester of pregnancy is associated with a reduced incidence of recurrent wheeze in the newborn infant.⁴

Assessment and Management

Assessment of asthma is divided into two domains, symptom control and future risk of adverse outcomes (e.g. exacerbations, airflow limitations, and medication side effects).⁵ Other guidelines, such as the Guidelines for the Diagnosis and Management of Asthma (EPR-3) by the National Heart, Lung and Blood Institute have produced assessment tools useful for classifying severity and level of asthma control for both children and adults.⁶ These charts are particularly useful for the initial classification of asthma severity in addition to assessing level of control. For the purposes of this review, the 2018 Global Strategy for Asthma Management and Prevention from the Global Initiative for Asthma (GINA 2018) will be the primary focus. According to GINA 2018, initial asthma severity can be classified as mild, moderate, or severe. Assessing the level of control for follow-up visits can be classified as well-controlled, partially-controlled, or uncontrolled.⁵ While evaluating literature regarding the management of asthma it is important to note that there is variance in organizational recommendations about the assessment and classification of asthma. Depending on the study, there may be slight variance among asthma severity and phenotype depending upon how the study was conducted and which guidelines were referenced.

ACRONYM KEY

- Anti-IgE = anti-immunoglobulin E
- Anti-IL5 = anti-Interleukin-5
- CFC = chlorofluorocarbon
- DPI = dry-powder inhaler
- EPR-3 = Expert Panel Report – Guidelines for the Diagnosis and Management of Asthma
- FEV1 = 1-second forced expiratory volume
- GINA = Global Initiative for Asthma
- HFA = hydrofluoroalkane
- ICS = inhaled corticosteroid
- LABA = long-acting beta-agonist
- LAMA = long-acting muscarinic antagonist
- LM = leukotriene modifier
- LTRA = leukotriene receptor antagonist
- MDI = metered-dose inhaler
- OCS = oral corticosteroid
- OTC = over-the-counter
- PRN = as needed
- SABA = short-acting beta-agonist
- SIT = single inhaler therapy
- SOB = shortness of breath
- TSLP = Thymic stromal lymphopoietin

According to GINA 2018, assessing level of symptom control relies on the following parameters:

- Daytime symptoms more than twice per week
- Any nighttime awakening due to asthma
- Use of reliever inhaler more than twice per week
- Limitation in activities due to asthma.

Patients are well-controlled if they do not meet any of the criteria, are partly controlled if they possess 1-2 of the criteria and are uncontrolled if they possess 3 or all of the criteria.⁵

There are numerous, modifiable risk factors to consider even in patients who otherwise have few asthma symptoms. They are summarized in Table 2.⁵

TABLE 2. Risk Factors for Poor Asthma Control⁵

<p><i>Having any of these risk factors increases the patient's risk of exacerbations, even in the presence of few asthma symptoms</i></p>	ICS not prescribed, poor adherence, incorrect technique
	High SABA use
	Low FEV1 (especially <60% predicted)
	Higher bronchodilator reversibility
	Major psychological or socioeconomic problems
	Smoking or allergen exposure
	Presence of obesity, chronic sinusitis, confirmed food allergy
	Sputum or blood eosinophilia
	Pregnancy

ICS: inhaled corticosteroid; SABA = short-acting beta-agonist; FEV1 = 1-second forced expiratory volume
**Adapted with permission from the GINA 2018 guideline update Box 2-2, page 29.*

Therapeutic Approach to Asthma Control and Risk Reduction

A stepwise approach should be used after assessment of a patient's asthma control. The stepwise approach consists of increasing or decreasing the dose and/or number of medications and frequency of administration as level of control worsens or improves. Several strategies exist for stepping up or stepping down therapy, however, guidelines agree that periodic medication adjustments that are most beneficial for the patient and provider are warranted. For example, according to GINA 2018 it is acceptable to either increase the dose of an ICS or maintain the current dose of an ICS and add a long-acting beta-agonist (LABA) for patients with uncontrolled asthma. Table 3 provides a summary of the treatment considerations for each step of therapy.

TABLE 3. Stepwise Approach to Asthma Treatment⁵

Severity Classification	STEP in Therapy	Preferred Controller Medication	Alternative Controller Medication
Mild	STEP 1	N/A	Low-dose ICS
	STEP 2	Low-dose ICS	LTRA
Moderate	STEP 3	Low-dose ICS + LABA	Medium/high-dose ICS OR Low-dose ICS + LTRA
		Medium/high-dose ICS + LABA or theophylline	Add tiotropium OR Medium/high-dose ICS + LTRA or theophylline
Severe	STEP 4	Medium/high-dose ICS + LABA or theophylline	Add tiotropium OR Medium/high-dose ICS + LTRA or theophylline
	STEP 5	Specialist referral for add-on controller treatment methods*	Add low-dose OCS

ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid
**Tiotropium, anti-immunoglobulin E (anti-IgE), or anti-Interleukin-5 (anti-IL5) treatment options recommended based on patient characteristics and provider recommendation*

Available Asthma Reliever Medications

Short-Acting Beta Agonists (SABA) - A staple of asthma therapy consists of reliever medications intended to relieve asthma symptoms acutely. Commonly available SABA options include albuterol (ProAir®, Proventil®, Ventolin®) and levalbuterol (Xopenex®). SABAs work by relaxing bronchial smooth muscle tissue leading to bronchodilation. Table 4 summarizes key points when considering SABA use.

ProAir Respiclick® is a novel device that eliminates the need for actuation by using dry powder as opposed to a propellant.⁷ For this reason, the ProAir Respiclick® can't be used with a spacer. This is a key difference that should be communicated with patients when they are transitioned from the ProAir HFA® inhaler to the ProAir Respiclick® inhaler.

SABAs can cause tremors, shakiness, palpitations, hypokalemia, tachycardia, and hyperglycemia. Patients should

be educated to monitor for symptom frequency, days of SABA use, and use of peak flow. A peak flow meter is a handheld device that measures how well air moves out of a patient's lungs. During periods of worsening asthma, airways narrow and the patient's peak flow reading decreases. Clinicians can consider monitoring blood pressure, heart rate, plasma glucose, and serum potassium.

Most MDIs should be shaken and primed before first use and generally must

be re-primed after 7-14 days of no use, depending on the specific inhaler.⁸

Low-Dose ICS + Formoterol - For patients with moderate-to-severe asthma, or who are not well controlled on inhaled corticosteroid (ICS) monotherapy, a combination of low-dose budesonide + formoterol (Symbicort[®]) can be used as both a reliever therapy and maintenance therapy, referred to as single-inhaler therapy (SIT). For example, patients could be prescribed Symbicort[®] to be used twice daily as a maintenance inhaler, with instructions to also use PRN as a reliever therapy. According to a systematic review published in 2013 by Cates and Karner, SIT with budesonide and formoterol can reduce the risk of asthma exacerbations requiring the need for oral corticosteroids. However, the studies included adults ≥ 18 years of age, thus precluding the use of single-inhaler therapy in children. There were higher rates of discontinuation among uses of single-inhaler therapy and has little impact on rates of hospitalization.⁹ More information regarding the Symbicort[®] inhaler can be found in the controller therapy section.

Available Asthma Controller Medications
Inhaled Corticosteroid (ICS)

Monotherapy - ICS inhalers are available as monotherapy or combination therapy, as well as dry-powder inhaler (DPI) or metered-dose inhaler (MDI) options. ICS therapy is considered the cornerstone of controller therapy for patients with asthma that is not well controlled and should be considered first-line. ICS therapy inhibits the inflammatory response of bronchial tissues and improves airflow.⁵

ICS therapy can cause dysphonia, oral candidiasis, hoarseness, and cough. High-dose ICS use has also been associated with an increased risk of pneumonia and growth suppression in children. Patients should be educated to rinse their mouth after using an inhaler with an ICS to reduce the risk for developing oral candidiasis, monitor for symptom frequency, days of SABA use and use of peak flow. Clinicians can consider monitoring for signs of oral candidiasis and suppressed growth in children taking high doses of ICS products.¹

When referring to the stepwise approach for medication therapy, one

TABLE 4. Available SABA Medications

Brand Name (available strengths)	Device	Typical Dosing	Dose Counter	Use with Spacer
Albuterol				
ProAir Digihaler [®] 117mcg	DPI	180 mcg every 4-6 hours PRN	Yes	No
ProAir Respiclick [®] 90mcg	DPI			
Ventolin [®] HFA 90mcg	MDI			Yes
Proventil [®] HFA 90mcg				
Albuterol sulfate HFA 90mcg	Nebulizer	1.25-5mg every 4-8 hours PRN	N/A	N/A
Albuterol Solution 0.63mg/3mL, 1.25mg/3mL, 2.5mg/3mL				
Levalbuterol				
Xopenex HFA [®] 45 mcg	MDI	90 mcg every 4-6 hours PRN	No	Yes
Levalbuterol HFA 45 mcg				
Levalbuterol Solution 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL	Nebulizer	0.31-1.25 mg every 4-06 hours PRN	N/A	N/A
<i>Information above can be found in more detail within each product's package insert HFA: hydrofluoroalkane; DPI: dry-powder inhaler; MDI: metered-dose inhaler; PRN: as needed</i>				

TABLE 5. Select ICS Potencies

Inhaled Corticosteroid	Age ≥ 12 Years			Age 5-11 Years		
	Low	Medium	High	Low	Medium	High
Beclomethasone (QVAR Redihaler [®])	80-240 mcg	280-480 mcg	>480 mcg	80-160 mcg	200-320 mcg	>320 mcg
Budesonide (HFA)	320 mcg	320-640 mcg	640 mcg	160 mcg		
Fluticasone furoate (Arnuity Ellipta [®])	100 mcg	N/A	200 mcg	50 mcg	50 mcg	50 mcg
Fluticasone furoate (Breo Ellipta [®])	100 mcg	N/A	200 mcg	Not approved for use		
Fluticasone propionate (Advair HFA)	176 mcg	264-440 mcg	>440 mcg	176 mcg	220-352 mcg	>352 mcg
Fluticasone propionate (Advair Diskus [®])	200-300 mcg	350-500 mcg	>500 mcg	100-200 mcg	>200-400 mcg	>400 mcg
Mometasone (Asmanex HFA)	220 mcg	330-440 mcg	>440 mcg	110 mcg	220-<440 mcg	>440 mcg
<i>Adapted from: Clinical Resource, Inhaled Corticosteroid Dose Comparison in Asthma. Pharmacist's Letter/Prescriber's Letter. March 2019.</i>						

must consider the ICS dose in terms of low, medium or high dose. Table 5 lists the dosing classification for commonly used ICS medications.¹⁰ The list is not all

inclusive and only contains information on the ICS component if available in a combination inhaler.

Monotherapy ICS options are depicted

TABLE 6. Available Monotherapy ICS Products

Brand Name (available strengths)	Device	Typical Dosing	Dose Counter	Use with Spacer
Beclomethasone				
QVAR Redihaler® 40 mcg, 80 mcg	MDI	40-320 mcg BID	Yes	No
Budesonide				
Pulmicort Flexhaler® 90 mcg, 180 mcg	DPI	180-720 mcg BID	Yes	No
Pulmicort Respules® 0.25, 0.5, 1mg/2mL	Nebulizer	0.25-1 mg Q6H	N/A	N/A
Fluticasone				
Flovent HFA 44 mcg, 110mcg, 220 mcg	MDI	88-880 mcg BID	Yes	Yes
Flovent Diskus® 50mcg, 200mcg, 250mcg	DPI	50-250 mcg BID	Yes	No
Arnuity Ellipta™ 100mcg, 200mcg	DPI	100-200 mcg QD	Yes	No
Armonair Respiclick® 55mcg, 113mcg, 232mcg	DPI	55-232 mcg BID	Yes	No
Mometasone				
Asmanex HFA 100mcg, 200mcg	MDI	100-400 mcg BID	Yes	Yes
Asmanex Twisthaler® 110mcg, 220mcg	DPI	220-440 mcg BID	Yes	No
*Information above can be found in more detail within each product's package insert				

in Table 6. Updates to inhaler devices include the addition of the Ellipta® inhaler. Arnuity Ellipta® is a once daily ICS that contains fluticasone. Comparatively, Flovent Diskus® is a twice daily ICS also containing fluticasone. The once daily administration of the Ellipta® device may improve patient compliance and ultimately the patient's level of asthma control, although no head-to-head trials have been completed. Additionally, the Ellipta® device may have a simpler design which requires the patient to perform less steps to correctly use; however, this has not been evaluated in any studies.

The Redihaler® device is available as a replacement the HFA inhaler for QVAR®. The Redihaler® is an MDI which is slightly different than the traditional MDI. For this device, the patient does not actuate the device by pressing a button, rather it is the force of inspiration that activates the device to deliver a dose.¹¹ Currently, QVAR® is

the only available inhaler that utilizes the Redihaler® device.

Inhaled-Corticosteroids (ICS) + Long-Acting Beta-Agonist (LABA) Combination Therapy - For patients with moderate or severe asthma, consideration should be given to adding a LABA to the patient's current therapy that already includes an ICS. Similar to ICS therapy, LABAs relax bronchial smooth muscle leading to bronchodilation. However, there is concern that chronic exposure to LABAs is associated with tolerance and reduced sensitivity to the bronchodilator effect. LABAs should therefore not be used as monotherapy for the maintenance treatment of asthma due to an increased risk of death, but still can be used in combination with an ICS.¹² Available ICS/LABA combinations are summarized in Table 7.

As mentioned previously under monotherapy ICS devices, the Ellipta®

device (such as Breo Ellipta®) is a once daily maintenance combination therapy option compared to the Advair® products which are all twice daily. One will notice the replacement of salmeterol/fluticasone propionate in Advair® with vilanterol/fluticasone furoate in Breo®. Studies have shown that this novel combination when used once daily can reduce the frequency of asthma exacerbations compared to placebo, but was not significantly different than traditional twice daily dosing of salmeterol/fluticasone.¹³

Long-Acting Muscarinic Antagonist (LAMA) Therapy - For patients with moderate-to-severe asthma, a LAMA can be used as a controller medication, often in addition to ICS/LABA combination controller therapy. For use in the treatment of asthma, tiotropium inhibits muscarinic receptors on smooth muscle causing bronchodilation. Although limited, there are high-quality studies assessing the effect of LAMAs on asthma control. One systematic review published in 2015 found that adding tiotropium to existing ICS therapy rather than increasing ICS dose may improve surrogate markers, such as lung function, but have not been shown to improve patient-oriented outcomes such as hospitalizations from asthma exacerbations, presentation to the emergency department, control of asthma or quality of life.¹⁴

Tiotropium is available as the Spiriva Respimat® soft mist inhaler device. It is important to note that the Spiriva Handihaler® device and capsules have not been approved for the treatment of asthma. Daily doses greater than 2.5 mcg have not been shown to confer additional benefit. Care should be given to prescribing and dispensing as the Spiriva Respimat® inhaler is available in concentrations of 1.25 mcg/actuation (asthma) and 2.5 mcg/actuation (COPD). The Respimat® inhaler utilizes a unique delivery system to deliver a soft, gentler mist rather than a forceful spray. Therefore, it is unable to be used with a spacer. However, this technology could improve the deposition of medication into the lungs, rather than the mouth and throat because of the reduced propellant velocity. The Respimat® device includes a dose counter and requires assembly as the medication canister is provided separate from the delivery device. Patients should be

educated on the proper assembly and use of the device.

Non-Inhaler Asthma Controller Medications

Leukotriene Modifiers (LMs) - There are also non-inhaled controller medications available for patients suffering from severe asthma. Leukotriene modifiers include medications that block the leukotriene receptors (LTRAs) and those which inhibit 5-lipoxygenase. Available LTRAs include the orally active medications zafirlukast and montelukast. A newer medication, zileuton, is available and targets the 5-lipoxygenase enzyme which is primarily responsible for the formation of leukotrienes. All of these medications are orally active and provide patients with severe asthma a specialized treatment option when other forms of therapy have been exhausted. Advantages of these medications include oral administration and few side effects for most patients. Although there is data to support use, guidelines still note that LTRAs/LMs are considered less effective than ICS medications.⁵ These medications may be useful in patients who struggle or are unwilling to use inhalers, have experienced side effects with ICS use, or have concomitant allergic rhinitis as an initial controller option in mild asthma. It may also be considered as add on therapy in moderate or severe asthma though the effectiveness is limited.¹⁵

Theophylline - Theophylline remains a recommended treatment option in some patients with moderate or severe asthma as add-on therapy to control symptoms and reduce risk of exacerbation. It is not recommended for the management of asthma in children or for those with mild symptoms. Theophylline is a therapy that has fallen out of favor in current guidelines for asthma treatment due to its limited efficacy, narrow therapeutic window for treatment, difficulty to manage, and possible toxicity related to use.⁵ For patients who require theophylline use in asthma control, it is best that they be managed closely by their provider. Current guidelines recommend exhaustion of most other possible alternatives before using in this condition for adolescents or adults.^{5,15}

TABLE 7. Available Combination ICS/LABA Inhalers

<i>Brand Name (available strengths)</i>	<i>Device</i>	<i>Typical Dosing</i>	<i>Dose Counter</i>	<i>Use with Spacer</i>
<i>Salmeterol/fluticasone propionate</i>				
Advair Diskus® 50 mcg/100 mcg 50 mcg/250 mcg 50 mcg/500 mcg	DPI	1 inhalation BID	Yes	No
Advair HFA 21 mcg/45 mcg 21 mcg/115 mcg 21 mcg/230 mcg	MDI	2 inhalation BID	Yes	Yes
AirDuo Respiclick® 14 mcg/55 mcg 14 mcg/113 mcg 14 mcg/232 mcg	DPI	1 inhalation BID	Yes	No
<i>Vilanterol/fluticasone furoate</i>				
Breo Ellipta™ 25 mcg/100 mcg 25mcg/ 200 mcg	DPI	1 inhalation once daily	Yes	No
<i>Formoterol/budesonide</i>				
Symbicort HFA 4.5 mcg/80 mcg 4.5 mcg/160 mcg	MDI	2 inhalations BID	Yes	Yes
<i>Formoterol/mometasone</i>				
Dulera HFA 5 mcg/100 mcg 5 mcg/200 mxg	MDI	2 inhalations BID	Yes	Yes

**Information above can be found in more detail within each product's package insert*

Newer Medications in the Management of Asthma

Although new therapies are constantly being discovered, the diagnosis and step-wise approach of treatment has been generally consistent from previous guidelines. Changes in therapy recommendations are mostly seen for those patients who present with “severe” (“treatment-resistant” or “refractory”) forms of asthma, or those with specific asthma diagnoses requiring specialist intervention. The emergence of breakthroughs in biologic therapies have given a new treatment option for patients with “treatment-resistant” or “refractory” asthma. Recently, there has also been a reintroduction of a previously available agent used for asthma relief over-the-counter. Some of the newly FDA-approved products can be noted in the following sections and Table

8. Although this list is not exhaustive, it highlights those products that officially carry an indication of asthma. With the discovery of these newer controller agents, providers may be able to minimize use of regular high-dose corticosteroids (oral or inhaled) and improve daily control of symptoms for patients while reducing risk for exacerbation. There are also several pipeline therapies and other non-drug methods which are emerging as popular treatments in certain asthma diagnoses. One example is sublingual immunotherapy for those suffering from asthma related to allergen exposure.^{5,16,17}

Epinephrine Inhalation Aerosol (Primatene® Mist)

Primatene® Mist is now the only available OTC inhaler on the market. It acts as a bronchodilator to open the airways and is specifically indicated for the relief of mild symptoms associated

TABLE 8. New and Emerging FDA Approved Treatments for Asthma

Medication Name	FDA Approval Date	Dosing & Administration	Mechanism of Action	Role in Asthma Treatment
Epinephrine (Primatene® Mist)	Nov 8, 2018	<ul style="list-style-type: none"> Dose: 0.125 mcg/spray Route: HFA inhaler 	Bronchodilator (relaxation of bronchiole smooth muscle)	<ul style="list-style-type: none"> Patients ≥12 years Mild, intermittent asthma OTC use for acute symptom relief with provider oversight
Benralizumab (Fasenra™)	Nov 14, 2017	<ul style="list-style-type: none"> Dose: 30 mg SubQ injection every 4 weeks for 3 doses, then once every 8 weeks Route: Pre-filled syringe 	Monoclonal antibody IL-5R-α antagonist	<ul style="list-style-type: none"> Patients ≥12 years Severe, eosinophilic asthma Add-on maintenance therapy
Dupilumab (Dupixent®)	Oct 19, 2018	<ul style="list-style-type: none"> Dose: 400 mg SubQ injection for 1 dose, then 200 mg once every 2 weeks Route: Pre-filled syringe 	Monoclonal antibody IL-4/IL-13 antagonist	<ul style="list-style-type: none"> Patients ≥12 years Severe, eosinophilic asthma OR corticosteroid dependent asthma Add-on maintenance therapy
Tezepelumab* (AMG 157)	Sept 12, 2018	<ul style="list-style-type: none"> Dose: 70 mg or 210 mg SubQ injection every 4 weeks, or 280 mg every 2 weeks Route: Unestablished 	Monoclonal antibody TSLP antagonist	<ul style="list-style-type: none"> Patients 18-75 years old** Severe asthma, ICS/LABA with or without oral corticosteroids and additional asthma controllers Add-on maintenance therapy

Information above can be found in more detail within each product's package insert
**Granted approval on breakthrough designation by the FDA, and does not currently have a brand name associated with the product*
***Based on study population from Phase 2 trial, only patients between 18 and 75 years were included*

with intermittent asthma in patients ≥12 years, and only for those who have been diagnosed with asthma by a health care provider.¹⁸ It is dosed as one inhalation (0.125 mcg/inhalation) of epinephrine as needed for symptom relief with at least 1 minute between repeat inhalations, and a maximum of 8 inhalations in 24 hours. The FDA recommends patients see a doctor if asthma is not better within 20 minutes of use, if symptoms gets worse, if more than eight inhalations are needed in a 24-hour period, or if they experience more than two asthma attacks in a week.

Primatene® Mist was originally approved for OTC use by the FDA in 1967 as an treatment for asthma symptoms before being taken off the market in 2011 for containing chlorofluorocarbon (CFC) propellants.^{19,20} Recently, the manufacturer

of the product reformulated the device to contain HFA propellant, a widely accepted mechanism that is used by a number of prescription inhalers. The FDA re-approved Primatene® Mist in the new formulation on November 8th, 2018 despite pushback from some national organizations citing the dangers of patients potentially attempting to self-treat a serious chronic condition associated with high healthcare burden and that all patients with asthma should be under the guidance of a healthcare professional.²⁰ Primary concerns seem to be related to possible side effects related to use, potential for unregulated use of an OTC product, self-diagnosis of asthma by patients, and delay of medical care due to symptom control. The FDA clearly states that this product is only for use within specific patients who may

require immediate relief, who have been diagnosed with asthma, and are being managed by their healthcare provider. It may be advisable for pharmacies to keep Primatene® Mist behind the counter so that patients who purchase the product can be properly educated.²²

Benralizumab (Fasenra™)

Benralizumab is an anti-IL5 monoclonal antibody medication that specifically targets IL-5 and blocks it from binding to receptor-α (IL-5R-α). This product was FDA approved in November 2017 as 30 mg subcutaneous injections every 4 weeks for 3 doses, then continued once every 8 weeks for add-on maintenance treatment of patients with severe asthma ≥12 years with an eosinophilic phenotype. Studies of benralizumab have demonstrated a decrease in asthma exacerbations in severe eosinophilic asthma.^{17,23} Previous guidelines have made note of other available anti-IL5 monoclonal antibody products such as mepolizumab (subcutaneous injection) and reslizumab (intravenous injection), with newer guidelines now including benralizumab as another add-on maintenance therapeutic option following successful trials in use for the treatment of asthma and prevention of exacerbations. Phase 2b trials saw significant reductions in the occurrence of asthma exacerbation of up to 57% compared to placebo in patients with an elevated baseline eosinophil count.^{23,24} Early studies of this medication class produced varying results in terms of efficacy in treatment, but current evidence shows they are effective in patients who have elevated eosinophil levels and severe asthma. Possible common side effects include pharyngitis and headaches and patients who are taking corticosteroids should not abruptly discontinue steroid therapy while taking this medication. Based on current recommendations and evidence, therapy with benralizumab (and other anti-IL-5 agents) is best reserved for add-on maintenance treatment in the setting of severe asthma, specifically targeting eosinophil-high patients.

Dupilumab (Dupixent®)

Dupilumab is an anti-IL4 and anti-IL13 monoclonal antibody medication that specifically binds to and blocks the IL-4R-α

subunit. This medication was initially approved by the FDA in March 2017 for the treatment of moderate-to-severe atopic dermatitis not controlled by topical products. In October of 2017 it received an additional indication for the treatment of patients ≥ 12 years with moderate to severe eosinophilic asthma or patients with oral corticosteroid dependent asthma.²⁰ Dupilumab is dosed depending on the asthma diagnosis and step in therapy. In patients requiring add-on maintenance therapy for moderate-severe asthma, an initial subcutaneous injection of 400 mg is followed by injection of 400 mg followed by 200 mg injections every two weeks. For patients with corticosteroid dependent asthma, or those with concomitant atopic dermatitis, a higher initial dose of 600 mg is used initially followed by 300 mg every two weeks. In a randomized prospective study evaluating patients with moderate-to-severe asthma for use in asthma treatment, dupilumab exhibited significant reductions in asthma exacerbations (6% dupilumab group vs. 44% placebo group), as well as improvements in other clinical outcomes including quality of life and lung function.^{17,25} It is currently the only therapy in this class that carries an FDA approval for use in the treatment of asthma. As with other monoclonal antibodies used in the treatment of asthma, this medication is best utilized for targeting specific patients who require additional maintenance therapy in the setting of eosinophil-high patients.

Tezepelumab (AMG 157)

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that acts as an upstream modulator of inflammatory pathways. Patients with asthma generally demonstrate a higher level of TSLP than those of healthy individuals, making it a possible target of treatment.^{26,27} Tezepelumab (also known as AMG 157) is an anti-TSLP monoclonal antibody medication, and the first of its kind utilized for the treatment of asthma. By blocking TSLP, it is thought that the release of pro-inflammatory cytokines will be diminished causing a reduction in asthma exacerbations. In Phase II trials, tezepelumab demonstrated efficacy in reduction of exacerbation rate compared to placebo over a 52-week study period.

Three maintenance doses (70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks) of this medication, all administered as subcutaneous injection, were evaluated, and demonstrated a reduction in clinically significant asthma exacerbations based on the calculated annualized asthma exacerbation rate (events per patient year) when added to long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids at all doses. When comparing the evaluated maintenance doses exacerbation rates were reduced in the low- (0.26), medium- (0.19), and high-dose (0.22) groups compared to placebo (0.67). This translated to a relative reduction of asthma exacerbations by 61%, 71%, and 66% for the respective doses.²⁸ The most common adverse effects reported in the trial were asthma-related nasopharyngitis, headaches, and bronchitis. Currently this medication is undergoing Phase III trials but was granted breakthrough designation by the FDA in September 2018, opening the door for a new mechanism in the treatment of asthma. This medication will likely be best for a wider spectrum of patients suffering from severe asthma and who currently are uncontrolled with use of ICS/LABA maintenance therapy with or without oral corticosteroids, and is not restricted to use for patients with an eosinophilic asthma phenotype.

Conclusion

Asthma can be an extremely trying condition for patients to manage with a high healthcare burden. Pharmacists have the opportunity to impact patients through knowledge and education about available products and understanding about how prescribers may approach the management of asthma in their patients. Although treatment guidelines have remained consistent in recent years, there are new medications and devices emerging to enhance efficacy and safety of our therapeutic options. It is important that pharmacists are familiar with these new products and devices so that patients can be appropriately counseled regarding administration and drug information pertinent to their care. Currently, many of the new products emerging are utilizing new mechanisms of treatment. Although newer monoclonal antibody biologics have

focused on patients with severe asthma to this point, there may be opportunities in the future for expanded use.

Zachary Pape is an Assistant Professor of Clinical Sciences at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Nathan Lamberton is an Assistant Professor of Clinical Sciences at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI.

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts and honoraria.

References

1. (EPR-3), E. P. R. 3. (2007). Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *Journal of Allergy and Clinical Immunology*, 120(5), s94-138. Accessed March 29, 2019.
2. National Center for Health Statistics. Centers for Disease Control and Prevention. <https://www.cdc.gov/nchs/nhis/index.htm>. Updated February 6, 2019. Accessed February 6, 2019.
3. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest*. 2005;127(2):502-508.
4. Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016;375(26):2530-2539.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2018. Vancouver, USA GINA; 2018.
6. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(suppl 5):S94-138.
7. ProAir Respiclick® (albuterol sulfate) [package insert]. Horsham, PA: Teva Respiratory LLC; 2018.
8. Clinical Resource, Correct Use of Inhalers. Pharmacist's Letter/Prescriber's Letter. January 2017. Accessed February 6, 2019.
9. Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2013;(4):CD007313.
10. Clinical Resource, Inhaled Corticosteroid Dose Comparison. Pharmacist's Letter/Prescriber's Letter. August 2009. Accessed February 6, 2019.
11. RediHaler®. National Jewish Health. <https://www.nationaljewish.org/treatment-programs/medications/inhaled-medication-asthma-inhaler-copd-inhaler/metered-dose/redihaler>. Accessed February 22, 2019.

NOT FOR REPRODUCTION

12. Morales DR. LABA monotherapy in asthma: an avoidable problem. *Br J Gen Pract.* 2013;63(617):627-628.

13. Albertson TE, Richards JR, Zeki AA. The combination of fluticasone furoate and vilanterol trifenatate in the management of asthma: clinical trial evidence and experience. *Thorax.* 2015;10(1):43-56.

14. Evans DJ, Kew KM, Anderson DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma. *Cochrane Database Syst Rev.* 2015;(7):CD011437.

15. Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients: diagnosis and management. Published November 2018. Accessed February 20, 2019.

16. Drug Guide | AAAAI. The American Academy of Allergy, Asthma & Immunology. <https://www.aaaai.org/conditions-and-treatments/drug-guide>.

17. Kim AS, Doherty TA. New and emerging therapies for asthma. *Ann Allergy Asthma Immunol.* 2016;116(1):14-17.

18. Over the Counter Asthma Medicine – Mild Symptoms. Home. <https://www.primatene.com/otc-asthma-medicine.aspx>. November 2018. Accessed February 8, 2019.

19. American College of Chest Physicians disagrees with FDA decision to approve over-the-counter epinephrine for the treatment of asthma. American College of Chest Physicians. <http://www.chestnet.org/News/Press-Releases/2018/11/OTC-Epinephrine>. November 2018. Accessed February 8, 2019.

20. Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016126>. Accessed February 8, 2019.

21. Safely using the newly available OTC asthma inhaler Primatene Mist. US Food & Drug Administration. <https://www.fda.gov/Drugs/NewsEvents/ucm624994.htm>. November 2018. Accessed February 8, 2019.

22. Article, ensure safe use of OTC Primatene Mist for asthma, Pharmacist's Letter, Published January 2019. Accessed February 8, 2019.

23. Castro M, Wenzel SE, Bleeker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med.* 2014;2(11):879-890.

24. Krug N, Hohfeld JM, Kirsten A, et al. Allergen-induced asthmatic responses modified by a GATA3-Specific DNzyme. *N Engl J Med.* 2015;372(21):1987-1995.

25. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013;368(26):2455-66.

26. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol.* 2015;135(2):299-310.

27. Tezepelumab granted breakthrough therapy designation by US FDA for the treatment of patients with severe asthma without an eosinophilic phenotype. AMGEN. <https://www.amgen.com/media/news-releases/2018/09/tezepelumab-granted->

breakthrough-therapy-designation-by-us-fda-for-the-treatment-of-patients-with-severe-asthma-without-an-eosinophilic-phenotype/

Published September 2018. Accessed February 20, 2019.

28. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med.* 2017;377(10):936-946.

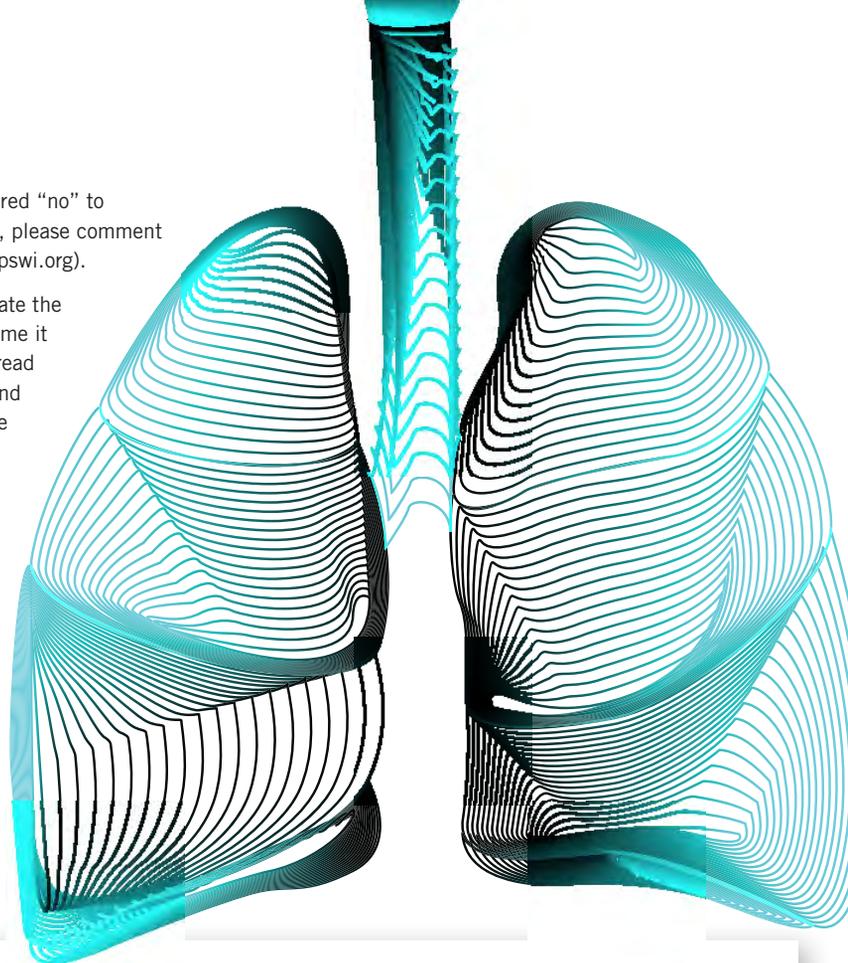
Assessment Questions

- Which of the following risk factors are associated with poor asthma control?
 - Assessment of inhaler technique
 - High FEV1
 - Infrequent SABA use
 - Obesity
- According to GINA 2018, patients with moderate severity asthma would be indicated for what STEP of therapy?
 - STEP 1
 - STEP 2
 - STEP 3
 - STEP 4
 - STEP 5
- True or False:** The Resplick[®] inhaler device should be used with a spacer.
 - True
 - False
- Which of the following is a key difference between the Breo Ellipta and Advair Diskus devices?
 - Breo Ellipta[™] is an MDI while Advair Diskus[®] is a DPI
 - Breo Ellipta[™] requires priming while Advair Diskus[®] does not require priming
 - Breo Ellipta[™] is dosed once daily while Advair Diskus[®] is dosed twice daily
 - Breo Ellipta[™] does not require priming while Advair Diskus[®] does require priming
 - Patient should rinse their mouth after using Breo Ellipta[™] but do not have to rinse after using Advair Diskus
- The recommended dosing of Spiriva Respimat[®] for the treatment of moderate-to-severe asthma is:
 - 1.25 mcg/act 1 puff by mouth once daily
 - 1.25 mcg/act 2 puffs by mouth once daily
 - 2.5 mcg/act 1 puff by mouth once daily
 - 2.5 mcg/act 2 puffs by mouth once daily
 - 1.25 mcg/act 1 puff by mouth twice daily
- Primatene[®] Mist is an OTC product reserved for use in the treatment of

asthma as:

- A reliever medication for mild asthma symptoms
 - A reliever medication for severe asthma exacerbations
 - A controller medication for mild asthma symptoms
 - A controller medication for moderate asthma symptoms
 - A controller medication for moderate asthma symptoms
- AP is a 22-year-old male with diagnosed "severe asthma". He is currently taking Breo Ellipta[™] 25mcg/ 200 mcg and using one inhalation daily. Recently he has been having 3-4 exacerbations per week that have required use of a reliever medication. His doctor measured his serum-eosinophil level and determined that it was "not-elevated". He is not currently using any other medications besides the Breo Ellipta[™] and his reliever inhaler. AP is most concerned about having to use another inhaler to control his symptoms and would prefer another route of administration if possible. Which of the following would be the most appropriate add-on therapy for AP?
 - Primatene[®] Mist
 - Montelukast
 - Dupilumab
 - Benralizumab
 - Theophylline
 - Spiriva Respimat[®]
 - Among the new and emerging therapeutic agents for the control and relief of asthma symptoms, which of the following serves as a controller treatment option for patients without the eosinophilic phenotype?
 - Primatene[®] Mist
 - Dupilumab
 - Tezepelumab
 - Benralizumab
 - Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
 - Yes
 - No
 - On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.
 - On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

12. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.
13. How useful was the educational material?
 - a. Very useful
 - b. Somewhat useful
 - c. Not useful
14. How effective were the learning methods used for this activity?
 - a. Very effective
 - b. Somewhat effective
 - c. Not effective
15. Learning assessment questions were appropriate.
 - a. Yes
 - b. No
16. Were the authors free from bias?
 - a. Yes
 - b. No
17. If you answered “no” to question 16, please comment (emailinfo@pswi.org).
18. Please indicate the amount of time it took you to read the article and complete the assessment questions.



CE FOR PHARMACISTS

Continuing Education Credit Information



The Pharmacy Society of Wisconsin is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Continuing education credit can be earned by completing the self-assessment questions. Questions may be completed online at www.pswi.org or by mailing completed answer form to PSW, 701 Heartland Trail, Madison, WI 53717. Participants receiving a score of 70% or better will be granted 1 hour (0.1 CEU) credit through CPE Monitor within 60 day of quiz completion. Accurate birth date (MMDDYY) and CPE Monitor ID must be provided in order to receive this credit as required by ACPE.

This CE offering is offered free-of-charge to all PSW members. Nonmembers are charged \$20 for each exam submitted to cover administrative costs.

Submit Your CE Online



Quiz Answer Form

circle one answer per question

- | | |
|----------------|-----------|
| 1) a b c d | 10) _____ |
| 2) a b c d e | 11) _____ |
| 3) a b | 12) _____ |
| 4) a b c d e | 13) a b c |
| 5) a b c d e | 14) a b c |
| 6) a b c d e | 15) a b |
| 7) a b c d e f | 16) a b |
| 8) a b c d | 17) _____ |
| 9) a b | 18) _____ |

May/June 2019

An Overview of Recommended Asthma Treatments with New and Emerging Medications for Use

ACPE Universal Activity Number:
0175-0000-19-110-H04-P

Target Audience: Pharmacists

Activity Type: Knowledge-based

Release Date: May 1, 2019

(No longer valid for CE credit after May 1, 2022)

Name _____ Designation (RPh, PharmD, etc.) _____

CPE Monitor # _____ DOB (MMDDYY) _____

Preferred Mailing Address _____

City _____ State _____ Zip _____

Is this your home or work address?