PDL Decision Process

- The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.

- A **Therapeutic Alternative** is defined by the AMA as: “drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses”\(^1\).

- The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.

- In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non-preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a “safety valve” in that it facilitates use of the most appropriate agent regardless of PDL status.

---

\(^1\) AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   Acceptable reasons include:
   - Allergy to medications not requiring prior approval
   - Contraindication to or drug-to-drug interaction with medications not requiring prior approval
   - History of unacceptable/toxic side effects to medications not requiring prior approval

2. The requested medication may be approved if both of the following are true:
   - If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
   - The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class within the Respiratory Agents is organized into the following sections when applicable:

BACKGROUND:
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

RECOMMENDATION:
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
BACKGROUND

- Asthma is a reversible, chronic inflammatory disease of the bronchial tubes. Inflammation of the air passages can cause recurrent episodes of breathlessness, chest tightness, coughing, and wheezing. In addition, inflamed airways may cause an increase in bronchial hyperresponsiveness or overreaction to various triggers (i.e. colds, allergies, cigarette smoke, and weather changes). This hyperresponsiveness causes a series of events involving muscle tightening around the bronchial tubes, bronchial wall swelling, and production of increased mucus. This reaction increases the narrowing of the bronchial tubes to further obstruct airflow.

- Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive, irreversible airflow obstruction due to chronic bronchitis or emphysema. Chronic bronchitis specifically causes intermittent airway inflammation and excessive mucus production which leads to frequent, prolonged episodes of productive cough. Emphysema is caused by the destruction of alveoli and distal airspaces resulting in decreased ventilation and a loss of the capillary network essential for perfusion.

- The short-acting beta₂-agonists (SABAs) relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchitis. Bronchodilation may additionally facilitate expectoration.

- FDA Approved Indications:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Reversible Bronchospasm</th>
<th>Prevention of EIB</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol CFC MDI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albuterol HFA MDI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albuterol inhalation solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol inhalation solution</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol HFA MDI</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>metaproterenol inhalation solution</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>metaproterenol MDI</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pirbuterol MDI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CFC=Chlorofluorocarbon; HFA=hydrofluoralkane; MDI=metered-dose inhaler; EIB = Exercise-induced bronchospasm

- The most common side effects seen with the SABAs include headache, nausea/vomiting, nervousness, palpitations, tachycardia, and tremor.
  - Although there are both beta₁ and beta₂ receptors in the heart, the latter are more predominant in the lungs where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of beta₂ specific agonists is preferred in the treatment of bronchospasm. To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

- Significant drug interactions for the SABAs include increased risk of ventricular arrhythmias with MAOIs or Tricyclic antidepressants (TCA), potential for severe bronchospasm in asthmatic patients with beta-blockers and potentiation of adrenergic effects with other adrenergic drugs.
• The 2007 guidelines from the National Heart Lung and Blood Institute (NHLBI) were updated to reflect a change in focus from asthma severity to asthma control. Asthma control is defined as no or minimal daytime symptoms; no limitations in activity; no nocturnal symptoms; no or minimal need for rescue medications; normal or near normal lung function and no exacerbations. In these guidelines, a five-step treatment approach is introduced that offers flexibility to “step-up” treatment when asthma is uncontrolled or “step-down” treatment when asthma is controlled. These new guidelines recommend treatment with SABAs only on an as-needed basis particularly if patients experience only occasional daytime symptoms of short duration. When symptoms are more frequent and/or worsen periodically, patients require regular controller therapy.

• Current guidelines from the American Academy of Allergy Asthma and Immunology (AAAAI) also recommend reserving SABAs for as needed use to relieve symptoms. They state that use of a SABA more than twice weekly may indicate the need to initiate or increase long-term control therapy.

• Bronchodilator medications are central to the symptomatic management of COPD. They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise and improve exercise performance. They are given either on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease. While SABAs can be used on an as needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.

  o Current treatment guidelines from the Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group state that SABAs should be used as needed for the majority of symptomatic patients with COPD. These agents may also be administered on a scheduled basis for those patients uncontrolled on ipratropium alone. These guidelines further state that all short-acting agents have similar efficacy and selection could be based on cost.

• None of the guidelines specify which SABA should be used; however, the following should be taken into consideration:

  o Metaproterenol is neither beta_2 selective nor as long acting as albuterol; therefore, it should not be considered for first-line therapy.
  o Pirbuterol is similar in both efficacy and safety to the generically available albuterol CFC inhalers, although it is somewhat less beta_2 selective.
  o Levalbuterol is the R-enantiomer form of albuterol. Current clinical trials with levalbuterol offer mixed results. The majority of available studies indicate that levalbuterol inhalation solution has similar efficacy with fewer adverse effects when given in equivalent doses to albuterol inhalation solution.

    ▪ A randomized, double-blind clinical trial comparing levalbuterol (0.31 mg and 0.63 mg) to racemic albuterol (1.25 mg and 2.5 mg) in pediatric asthma patients (n=338) ranging in age from 4-11 years found that levalbuterol 0.31 mg was no different from placebo with regards to changes in ventricular heart rate, QTc interval, or glucose. The more favorable side effect profile of levalbuterol at low doses suggests that it may have a potential benefit in the pediatric population.
  o Given recent efforts to phase out CFC-containing inhalers by the end of 2008 due to environmental concerns, most SABAs are now available as an HFA inhaler. There appears to be no difference in tolerability or efficacy between the two MDI types. Maxair® is a CFC containing product, but it will continue to be available in that formulation at least through the end of 2009.
RECOMMENDATION:
SABAs are the therapy of choice for relief of acute symptoms of asthma and prevention of EIB. Clinical guidelines from the NHLBI, AAAAI and Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group do not distinguish between the available SABAs when it comes to safety or efficacy. Due to the phasing out of CFC inhalers in response to environmental concerns, it is suggested that there be at least one HFA product available as preferred. Given the potential for fewer side effects with levalbuterol, it should be available for those with intolerance to albuterol products.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

REREVIEW: SHORT ACTING BETA₂ ADRENERGIC AGENTS, INHALED

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBUTEROL CFC³ QL (Compares to Proventil®⁴)</td>
<td>ACCUNEB® solution for inhalation (albuterol)</td>
</tr>
<tr>
<td>ALBUTEROL solution for inhalation QL (Compares to Proventil®⁴)</td>
<td>ALUPENT MDI® QL (metaproterenol)</td>
</tr>
<tr>
<td>MAXAIR AUTOHALER® QL (pirbuterol)</td>
<td>ALUPENT® QL solution for inhalation (metaproterenol)</td>
</tr>
<tr>
<td>VENTOLIN HFA® QL (albuterol HFA)</td>
<td>METAPROTERENOL® QL solution for inhalation (Compares to Alupent®⁴)</td>
</tr>
<tr>
<td></td>
<td>PROAIR® HFA QL (albuterol HFA)</td>
</tr>
<tr>
<td></td>
<td>PROVENTIL® QL (albuterol CFC)</td>
</tr>
<tr>
<td></td>
<td>PROVENTIL HFA® QL (albuterol HFA)</td>
</tr>
<tr>
<td></td>
<td>PROVENTIL® solution for inhalation (albuterol)</td>
</tr>
<tr>
<td></td>
<td>XOPENEX HFA® CC, QL (levalbuterol)</td>
</tr>
<tr>
<td></td>
<td>XOPENEX® NEBULIZER SOLUTION CC, QL (levalbuterol)</td>
</tr>
</tbody>
</table>

Quantity Limits

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol MDI</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Albuterol solution</td>
<td>120 vials/month</td>
</tr>
<tr>
<td>Alupent®</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Alupent® solution</td>
<td>180 vials/month</td>
</tr>
<tr>
<td>Maxair Autohaler</td>
<td>1 inhaler/month</td>
</tr>
<tr>
<td>Metaproterenol solution</td>
<td>180 vials/month</td>
</tr>
<tr>
<td>ProAir® HFA</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Proventil®</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Proventil HFA®</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Ventolin HFA®</td>
<td>2 inhalers/month</td>
</tr>
<tr>
<td>Xopenex HFA®</td>
<td>2 canisters/month</td>
</tr>
<tr>
<td>Xopenex® Nebulizer Soln</td>
<td>Up to 90 vials/month</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

Clinical Criteria
Xopenex HFA® MDI/Nebulizer Solution:
- No prior authorization required for beneficiaries ages 2 and under.
- Prior authorization is required for all beneficiaries ages 3 and older and will be approved for those experiencing side effects with albuterol or whose cardiovascular status is considered to be in severely deteriorating condition (in this situation, a trial of one other agent is not required).
References

REREVIEW: INHALED STEROIDS

BACKGROUND
• The inhaled corticosteroids (ICSs) decrease the metabolism of arachidonic acid (an anti-inflammatory compound), reduce proinflammatory prostaglandin and leukotriene synthesis and increase the number and responsiveness of beta-adrenergic receptors. In addition, the late phase reaction to allergies is blocked causing a reduction in airway hyperresponsiveness and inhibiting inflammatory cell migration and activation.
• All ICSs are FDA approved for asthma maintenance treatment as prophylactic therapy, and all, except budesonide, are also approved for systemic corticosteroid reduction.
• The most commonly reported side effects of ICSs include cough, headache, nausea, oral candidiasis, pharyngitis and upper respiratory infection (URI).
  o A detailed questionnaire sent to 2912 pediatricians and adult endocrinologists in the United Kingdom asked physicians to recall any cases of adrenal crisis suspected to be due to ICS use in asthma. Among 33 cases identified as acute adrenal crisis, 28 were reported in children and 5 were reported in adults. The children generally presented with acute hypoglycemia, while adults usually showed a more insidious onset characterized by lethargy and nausea. Thirty cases were associated with fluticasone, one with both fluticasone and budesonide, and two with beclomethasone. Almost all cases were associated with high doses of steroid; however, the majority of doses were still within accepted treatment recommendations.
  o Budesonide is the only agent in this class with a Pregnancy Category B. All other agents in this class are classified as Pregnancy Category C.
  o Inhaled corticosteroids are contraindicated as primary treatment for status asthmaticus or any other acute asthma episode.
  o Prolonged use of ICSs has the potential to reduce vertical growth. The Childhood Asthma Management Program (CAMP) trial, which compared budesonide with nedocromil and placebo in 1,041 children followed for 4 to 6 years, found a 1 centimeter difference between study groups at the end of treatment. This reduction was related to the dose and length of use of corticosteroids. These height changes are consistent with the NAEPP guidelines, which report an average reduction in height of 1 centimeter over the first year; however, this effect is not sustained and may be reversible.
There are limited head to head clinical trials that compare the agents within this class. However, numerous studies have shown ICSs to be superior to placebo.
  
  o An eight week, randomized, multicenter, placebo-controlled, double-blind, double-dummy study was conducted to compare the safety and efficacy of once daily mometasone 440 mcg, budesonide 400 mcg, and placebo in 262 patients with moderate persistent asthma. The percent change in FEV1 from baseline to final evaluable visit was used as the primary efficacy endpoint. The FEV1 endpoint was significantly greater (p<0.01) in the mometasone DPI group (8.9%) than in the budesonide DPI (2.1%) and placebo (-3.9%) groups. Secondary efficacy variables, including morning and evening peak expiratory flow rates, albuterol use, percentage of asthma symptom-free days, and physician evaluated response to therapy were found to be significantly improved in the mometasone DPI group compared to the budesonide DPI and placebo groups (p<0.05). Both active treatment groups were well tolerated. Conclusions regarding clinical superiority are hard to evaluate as the doses of budesonide were lower than generally recommended.

The 2007 guidelines from the NHLBI utilize a stepwise approach to managing persistent asthma. In addition to all asthmatic patients using a SABA inhaler on an as-needed basis; the following chart outlines the guidelines.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Birth to 4 years</th>
<th>Ages 5 to 11 years</th>
<th>Ages ≥ 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Intermittent</td>
<td>No daily meds needed</td>
<td>No daily meds needed</td>
<td>No daily meds needed</td>
</tr>
<tr>
<td></td>
<td>PRN SABA</td>
<td>PRN SABA</td>
<td>PRN SABA</td>
</tr>
<tr>
<td>Step 2 Persistent</td>
<td>Low dose ICS</td>
<td>Low dose ICS</td>
<td>Low dose ICS</td>
</tr>
<tr>
<td></td>
<td>Alternative: cromolyn or montelukast</td>
<td>Alternative: cromolyn, LTRA, nedocromil, or theophylline</td>
<td>Alternative: cromolyn, LTRA, nedocromil, or theophylline</td>
</tr>
<tr>
<td>Step 3 Persistent</td>
<td>Medium dose ICS</td>
<td>Low dose ICS AND LABA OR leukotriene receptor antagonist (LTRA) OR theophylline OR medium dose ICS</td>
<td>Low dose ICS AND LABA OR medium-dose ICS Alternatives: Low dose ICS AND either LTRA, theophylline or zileuton</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4 Persistent</td>
<td>Medium dose ICS AND LABA OR montelukast</td>
<td>Medium dose ICS AND LABA</td>
<td>Medium dose ICS AND LABA</td>
</tr>
<tr>
<td></td>
<td>Alternative: medium ICS AND either LTRA or theophylline</td>
<td>Alternative: medium ICS AND either LTRA or theophylline</td>
<td>Alternative: medium ICS AND either LTRA, theophylline or zileuton</td>
</tr>
<tr>
<td>Step 5 Persistent</td>
<td>High dose ICS AND LABA OR montelukast</td>
<td>High dose ICS AND LABA</td>
<td>High dose ICS AND LABA</td>
</tr>
<tr>
<td></td>
<td>Alternative: high dose ICS AND either LTRA or theophylline</td>
<td>Alternative: high dose ICS AND either LTRA or theophylline</td>
<td>Consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td>Step 6 Persistent</td>
<td>High dose ICS AND LABA OR montelukast AND oral steroids</td>
<td>High dose ICS AND LABA AND oral steroids</td>
<td>High dose ICS AND LABA AND oral steroids</td>
</tr>
<tr>
<td></td>
<td>Alternative: high dose ICS AND either LTRA or theophylline PLUS oral steroids</td>
<td>Alternative: high dose ICS AND either LTRA or theophylline PLUS oral steroids</td>
<td>Consider omalizumab for patients who have allergies</td>
</tr>
</tbody>
</table>
RECOMMENDATION:
Efficacy studies clearly show ICSs reduce symptoms, frequency and severity of asthma exacerbations. As a result, improvements in lung function and quality of life have been observed by asthmatic patients. The 2007 NHLBI guidelines list ICSs as the preferred treatment for patients with persistent asthma at every level of severity. Although differences exist between agents in the class in dosage frequency and number of inhalations required for each dose, all ICSs appear to be equally effective when given in equipotent dosages. In order to allow provider choice among the various agents and delivery systems, it is recommended that at least three unique agents be available.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

REREVIEW: INHALED STEROIDS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMANEX® QL (mometasone furoate powder for inhalation)</td>
<td>AEROBID® QL (flunisolide MDI)</td>
</tr>
<tr>
<td>AZMACORT® QL (triamcinolone acetonide MDI)</td>
<td>AEROBID-M® QL (flunisolide MDI)</td>
</tr>
<tr>
<td>FLOVENT HFA® QL (fluticasone propionate MDI)</td>
<td>AEROSPAN™ QL (flunisolide hemihydrate MDI)</td>
</tr>
<tr>
<td>FLOVENT DISKUS® QL (fluticasone propionate powder for inhalation)</td>
<td>PULMICORT FLEXHALER® QL (budesonide powder for inhalation)</td>
</tr>
<tr>
<td>FLOVENT ROTADISK® QL (fluticasone propionate powder for inhalation)</td>
<td>PULMICORT RESPULES® QL (budesonide suspension for inhalation)</td>
</tr>
<tr>
<td>QVAR® QL (beclomethasone dipropionate MDI)</td>
<td></td>
</tr>
</tbody>
</table>

Quantity Limits

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobid®, Aerobid-M®</td>
<td>3 inhalers/month</td>
<td></td>
</tr>
<tr>
<td>Aerospan™</td>
<td>2 inhalers/month</td>
<td></td>
</tr>
<tr>
<td>Asmanex®</td>
<td>1 inhaler/month</td>
<td></td>
</tr>
<tr>
<td>Azmacort®</td>
<td>2 inhalers/month</td>
<td></td>
</tr>
<tr>
<td>Flovent HFA®</td>
<td>2 inhalers/month</td>
<td></td>
</tr>
<tr>
<td>Flovent Diskus®</td>
<td>50mcg:2/day, 100mcg:4/day, 250 mcg:8/day</td>
<td></td>
</tr>
<tr>
<td>Flovent Rotadisk®</td>
<td>50mcg:2/day, 100mcg:4/day, 250 mcg:8/day</td>
<td></td>
</tr>
<tr>
<td>Pulmicort Flexhaler®</td>
<td>2 inhalers/month</td>
<td></td>
</tr>
<tr>
<td>Pulmicort Respules®</td>
<td>2 vials/day</td>
<td></td>
</tr>
<tr>
<td>QVAR®</td>
<td>2 inhalers/month</td>
<td></td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Clinical or Step Therapy

Pulmicort Respules® PA not required for recipients ages 6 and under.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION
REFERENCES

   http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf

REVIEW: LONG-ACTING INHALED BETA₂ ADRENERGIC AGENTS

BACKGROUND

• Bronchospasms are due to smooth muscle contraction resulting from airway obstruction in asthma and Chronic Obstructive Pulmonary Disease (COPD). Beta-agonists prevent bronchospasm by stimulation of adenyl cyclase, the enzyme that forms cyclic AMP from ATP. The increased levels of cyclic AMP cause relaxation of bronchial smooth muscle and inhibition of the release of inflammatory mediators.

• Arformoterol and formoterol nebulized solutions are indicated for the long-term maintenance treatment of bronchoconstriction in patients with COPD. They are not indicated for the acute treatment of COPD exacerbations or the management of asthma. Formoterol and salmeterol dry powder for inhalation (DPI) are indicated for the treatment of COPD, prevention of exercise induced bronchospasm (EIB) and the prevention and treatment of bronchospasm associated with asthma.

• The most common adverse effects resulting from the use of long-acting beta-agonists (LABAs) are headache, GI upset, nervousness, palpitations, tachycardia and tremor.
  o All of the LABAs carry similar black box warnings stating, “Long-acting beta₂ adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, only use LABAs as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or patients whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including a LABA. Data from a large, placebo-controlled US study that compared the safety of salmeterol or placebo added with the usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo).”
  o The LABAs should be used with caution in patients with cardiovascular disease, seizure disorders or thyrotoxicosis. All LABAs are Pregnancy Category C.
The cardiovascular adverse reactions of the LABAs may be potentiated by MAOIs, TCAs or drugs known to prolong the QTc interval. MAOIs should be discontinued for 14 days before initiation of a LABA. Caution should be used in patients who are treated with beta blockers and LABAs to prevent inhibition of the bronchodilatory effects of the LABAs. To minimize this interaction, patients should be treated with cardioselective beta blockers if treatment with a beta blocker is unavoidable such as with prophylaxis after MI. The hypokalemic effects of adrenergic agonists may be potentiated by the coinadministration of xanthine derivatives, steroids or diuretics, particularly potassium wasting diuretics.

- Formoterol and salmeterol have been compared head to head in 3 studies.
  - A double-blind, double-dummy, placebo-controlled, randomized, four-period crossover study was conducted involving 25 patients with asthma and a history of EIB defined as mean fall in FEV\textsubscript{1} of 31% from baseline. Exercise challenges were performed on 12 days at either 5, 30 or 60 minutes after inhalation of a single dose of formoterol 12 mcg, salmeterol 50 mcg, terbutaline 500 mcg or placebo. There was no difference between active treatments at any time in EIB (measured by maximum fall in FEV\textsubscript{1} or area under the curve); however, the onset of bronchodilation was slower after salmeterol compared to terbutaline (p=<0.05) and formoterol (p=<0.05). Formoterol showed significantly better bronchodilation than salmeterol (p=<0.05) at all time points between 5 and 60 minutes.
  - Twenty COPD patients participated in a crossover, randomized, double-blind, placebo-controlled study. Participants underwent pulmonary function testing and dyspnea evaluation in basal condition at 5, 15, 30, 60 and 120 minutes after administration of albuterol, formoterol, salmeterol or placebo. There was a greater increase in inspiratory capacity after bronchodilator administration in COPD patients with decreased baseline inspiratory capacity. Formoterol treated patients had the greatest increase in inspiratory capacity.
  - The effects of single doses of formoterol 12 and 24 mcg and salmeterol 50 and 100 mcg were compared in a randomized, double-blind, placebo-controlled, crossover study of 47 patients with moderate-to-severe COPD. The percentage change from baseline in FEV\textsubscript{1} the first hour after drug inhalation was greater for formoterol than for salmeterol.
- Arformoterol (15 mcg BID, 25 mcg BID, or 50 mcg BID via nebulizer) and salmeterol (42 mcg BID via MDI) were compared in a 12-week, double-blind, randomized, double-dummy, placebo-controlled trial including 717 COPD patients. Mean percentage change in FEV\textsubscript{1} from the predose value over 12 weeks was significantly greater with all three arformoterol doses. All groups, including placebo, had similar rates of adverse effects and COPD exacerbations.
- The mainstay of asthma therapy includes an inhaled glucocorticoid (ICS) and a LABA as controller medications. These agents improve lung function, reduce asthma symptoms, and reduce the need for SABAs as rescue medications. However, LABAs should never be used as monotherapy for controlling asthma. The 2007 guidelines from the NHLBI recommend that patients over the age of five with moderate persistent asthma or asthma not controlled by low-dose ICS be considered as candidates for the addition of a LABA or for increasing the dose of the ICS. Those patients with severe persistent asthma should be treated with both an ICS and a LABA. Long acting beta\textsubscript{2} agonists may be used for prevention of EIB; however, frequent use may disguise poorly controlled persistent asthma.
- Bronchodilators are also the mainstay of COPD treatment because they improve emptying of the lungs, reduce dynamic hyperinflation, and improve exercise performance. These agents do not modify the decline in lung function or the prognosis associated with COPD, but they can be used early in the disease on an as needed or on a scheduled basis as COPD progresses. The 2006 GOLD guidelines state SABAs are among the principal treatments for symptomatic management of COPD, but regular treatment using a LABA is more effective and convenient.
RECOMMENDATION:
Long acting beta\textsubscript{2} agonists are a mainstay in the treatment of both asthma and COPD. The 2007 guidelines from the NHLBI recommend a combination of a LABA and an ICS for patients who have moderate to severe persistent asthma (step 4 or higher in children < 4 years old, step 3 or higher in patients 5 and up). These guidelines also recognize the role of a LABA in the prevention of EIB; however, SABAs are preferred for frequent or chronic use. The 2006 GOLD guidelines state regular treatment using a LABA is more effective and convenient than a SABA for the symptomatic management of COPD. Neither of these clinical guidelines distinguishes between the available LABAs when it comes to safety or efficacy.

While proven effective, these agents may increase the risk of asthma-related death; therefore, they should only be used as additional therapy in patients with asthma who are uncontrolled on an ICS. Given the potential safety concerns associated with these agents, it is recommended that all agents in this class be subject to clinical criteria to ensure their appropriate use. The nebulized forms may be beneficial in patients who have difficulty synchronizing breath and actuation using the dry powder inhalers. For this reason, it is recommended that at least one nebulized formulation be available for individuals who have difficulty using a DPI.

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

REREVIEW: LONG-ACTING INHALED BETA\textsubscript{2} ADRENERGIC AGENTS

<table>
<thead>
<tr>
<th>REFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORADIL\textsuperscript{\textregistered} ST, QL (formoterol DPI)</td>
<td>BROVANA\textsuperscript{\textregistered} CC, QL (arformoterol inhalation solution)</td>
</tr>
<tr>
<td>SEREVENT DISKUS\textsuperscript{\textregistered} ST, QL (salmeterol DPI)</td>
<td>PERFOROMIST\textsuperscript{TM} CC, QL (formoterol inhalation solution)</td>
</tr>
</tbody>
</table>

Quantity Limits
Brovana\textsuperscript{\textregistered} 120 mL/month
Foradil\textsuperscript{\textregistered} 1 inhaler/month
Perforomist\textsuperscript{TM} 120 mL/month
Serevent Diskus\textsuperscript{\textregistered} 1 inhaler/month

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

Step Therapy for Serevent Diskus\textsuperscript{\textregistered} and Foradil\textsuperscript{\textregistered}

Serevent\textsuperscript{\textregistered} or Foradil\textsuperscript{\textregistered} will be approved if ONE of the following criteria are met:
- A diagnosis of asthma (step 3 or higher, or moderate persistent to severe persistent) and currently treated with an inhaled steroid and an inhaled short-acting beta agonist; OR
- A diagnosis of Exercise Induced Bronchospasm and a short-acting beta agonist has been tried and failed (note: a SABA should still be provided for acute relief of symptoms); OR
- A diagnosis of COPD

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

Clinical Criteria for Brovana\textsuperscript{\textregistered} or Perforomist\textsuperscript{TM}

Brovana\textsuperscript{\textregistered} or Perforomist\textsuperscript{TM} will be approved for individuals who meet the following criteria:
Recipient has tried and failed (or been intolerant to) treatment with salmeterol DPI or formoterol DPI, OR recipient has difficulty using a dry powder inhaler (DPI).
References


REVIEW: LONG-ACTING BETA₂ AGONIST/INHALED CORTICOSTEROID COMBINATIONS

BACKGROUND

- For the treatment of asthma at any age, it is recommended to add a long acting beta₂ agonist (LABA) to an inhaled corticosteroid (ICS) if the asthma cannot be controlled on an ICS alone. Therefore, two products are now available which combine an ICS and a LABA: fluticasone with salmeterol (Advair®) and budesonide with formoterol (Symbicort®).
- Salmeterol and formoterol selectively bind to the beta₂ receptors in bronchial smooth muscle resulting in bronchial relaxation and inhibition of the release of hypersensitivity mediators from mast cells. Corticosteroids, budesonide and fluticasone, decrease the metabolism of arachidonic acid and reduce the synthesis of proinflammatory prostaglandins and leukotrienes. Corticosteroids also increase the number and responsiveness of beta-adrenergic receptors, block the late-phase reaction to allergens, reduce airway hyperresponsiveness and inhibit inflammatory cell migration and activation.
- The combination LABA / ICS products are approved for the chronic treatment of persistent asthma. These agents should not be used for acute asthma exacerbations. The dry powder formulation (DPI) of fluticasone (250 mcg) and salmeterol (50 mcg) are also approved for the treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis.
- The most common adverse events associated with these combination products include cough, headache, nausea, oral candidiasis, pharyngitis and upper respiratory infection.
  - Both of these products carry a black box warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma related deaths observed in patients taking salmeterol in the Salmeterol Multi-center Asthma Research Trial (SMART).
Caution should be used in patients with hepatic impairment who take fluticasone/salmeterol due to possible accumulation of both active ingredients. This product should also be used cautiously in patients with milk allergy because the salmeterol component contains milk proteins. Formoterol has been associated with exacerbations of convulsive disorders, hypokalemia and thyrotoxicosis, and should be used cautiously in these patient populations. The steroid components may cause an inadequate adrenal response, bone mineral density loss or a small growth velocity reduction in children and adolescents. The beta agonist component may cause cardiovascular disorders such as palpitations or tachycardia due to stimulation of beta receptors in the heart.

- A randomized, double-blind, double-dummy study compared the efficacy of fluticasone/salmeterol (250/50 mcg BID) to budesonide/formoterol (200/6 mcg BID) in 688 adults with persistent asthma and a FEV₁ of 81% (CONCEPT trial). After 4 weeks on stable dosing both groups continued for an additional 48 weeks on either a stable dose of fluticasone/salmeterol or an adjustable dosing regimen of budesonide/formoterol that required either halving the dose and stepping up or down as indicated by the percentage of symptom-free days (primary endpoint), presence or absence of nocturnal awakenings due to asthma, frequency of rescue medication use or changes in morning peak expiratory flow (PEF). Patients receiving stable doses of fluticasone/salmeterol had a greater percentage of symptom-free days compared to those receiving adjustable budesonide/formoterol (p=0.034) and fewer emergency room visits or hospitalizations (p=0.008). Patients in the adjustable budesonide/formoterol group used an average of 1.8 inhalations daily with nearly 83% stepping down to one inhalation daily.

- A follow up to the CONCEPT trial looked at long-term efficacy as well as impact on health-related quality of life of the stable-dose regimen of fluticasone/salmeterol and the adjustable maintenance dosing regimen of budesonide/formoterol. The mean change from baseline in the Asthma Quality of Life Questionnaire’s (AQLQ) overall score was not statistically different between the two groups (p=0.121). However, a post hoc regression analysis did identify a statistically significant difference in AQLQ score at 28 (p=0.038) and 52 (p=0.009) weeks in favor of the fluticasone/salmeterol group.

- A randomized, double-blind, double-dummy, placebo-controlled trial was completed over a 12 week period to compare the efficacy and safety of budesonide/formoterol to budesonide, formoterol and placebo. Patients ≥12 years of age (n=596) with moderate to severe persistent asthma who were previously receiving an ICS were placed on budesonide 160 mcg BID. After two weeks, patients were randomized to the combo product (160/4.5 mcg BID), budesonide (160 mcg BID), formoterol (4.5 mcg BID), budesonide (160 mcg BID) + formoterol (4.5 mcg BID), or placebo BID. The primary efficacy endpoints were mean change from baseline of FEV₁ and mean change from baseline in 12-hour FEV₁. The results were similar for all outcomes measures in the budesonide/formoterol and the budesonide + formoterol groups. The combination showed greater improvement in FEV₁ than the budesonide, formoterol, or placebo groups (p=0.049). Fewer patients on the combined agents experienced worsening asthma symptoms (p≤0.025). All of the treatments had similar safety profiles.

- The 2007 NHLBI guidelines recommend the addition of a LABA to an ICS for those whose asthma cannot be controlled on an ICS alone. The 2007 GOLD guidelines suggest the addition of an ICS to a LABA for patients with severe COPD whose symptoms cannot be controlled on an as needed dosage of a SABA and a scheduled dose of a LABA.
RECOMMENDATION:
The combination of an ICS and LABA is a reasonable agent for the treatment of asthma and COPD. There is insufficient evidence to show that one combination product is superior to another; therefore, these agents are assumed to be therapeutically equivalent. The 2007 NHLBI guidelines recommend the addition of a LABA to an ICS for patients of all ages whose asthma is not controlled on an ICS alone. The 2007 GOLD guidelines suggest the addition of an ICS to a LABA for patients with severe COPD whose symptoms cannot be controlled on a LABA and an as needed SABA. Based on these guidelines and the current medical literature, it is recommended that the combination LABA/ICS agents be reserved for asthma patients who require frequent use of an inhaled short-acting bronchodilator while maintained on an optimal dose of an inhaled steroid, and for COPD patients who have symptoms despite optimal doses of a LABA.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: LONG-ACTING BETAl2 AGONIST/INHALED CORTICOSTEROID COMBINATIONS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>ADVAIR DISKUS® CC,QL (salmeterol/fluticasone DPI)</td>
</tr>
<tr>
<td></td>
<td>ADVAIR HFA® CC,QL (salmeterol/fluticasone MDI)</td>
</tr>
<tr>
<td></td>
<td>SYMBICORT® CC,QL (formoterol/budesonide MDI)</td>
</tr>
</tbody>
</table>

Quantity Limits
Advair® = 1/month
Symbicort = 1/month

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Advair®/Symbicort®
Advair®/Symbicort® will only be approved if ONE of the following criteria is met:
• For the treatment of asthma or the treatment of other reversible airway disease(s) where optimal doses of inhaled steroids are being used and breakthrough symptoms require frequent use of inhaled short-acting bronchodilators; OR
• For the treatment of COPD where optimal doses of a long-acting beta agonist are being used and symptoms are still uncontrolled.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION
References

REREVIEW: INHALED ANTICHOLINERGICS

BACKGROUND

- Ipratropium inhibits vagally mediated reflexes by antagonizing the action of acetylcholine on bronchial smooth muscle and preventing secretions in the nasal mucosa. Albuterol activates beta_2_ receptors on airway smooth muscle leading to smooth muscle relaxation. Two agents in this category, Combivent® and DuoNeb®, utilize the combination of ipratropium and albuterol. Tiotropium inhibits M(3) receptors at the smooth muscle promoting bronchodilation.

- Ipratropium and tiotropium are approved for the maintenance treatment of bronchospasm associated with COPD. The combination of albuterol and ipratropium is indicated for the treatment of bronchospasm associated with COPD in patients who require more than one bronchodilator.

- Ipratropium and the ipratropium/albuterol combination most commonly cause headache, dry mouth, GI upset, nervousness/tremor, palpitations or chest pain. The most common adverse events reported with tiotropium are dry mouth (16%) and anticholinergic type side effects such as constipation (4%) and blurred vision. Glaucoma and urinary retention/difficulty occurred in less than 1% of the tiotropium treated population.

- Combivent® is contraindicated in patients with hypersensitivity to soy lecithin or related food products such as soybean or peanut.

- All of these agents should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder neck obstruction due to their anticholinergic activities. Tiotropium should be used with caution in patients with renal impairment (CrCl ≤ 50 mL/min) as accumulation of drug may occur. Ipratropium is Pregnancy Category B while albuterol containing products and tiotropium are Pregnancy Category C.

- The cardiovascular effects of albuterol or albuterol containing products may be potentiated by MAOIs and TCAs if given concurrently; therefore, MAOIs should be discontinued for 14 days prior to starting therapy with albuterol or albuterol containing products. Tiotropium is metabolized via the cytochrome P450 3A4 and 2D6 isoenzymes; therefore, caution should be used if patients are taking tiotropium along with 3A4 or 2D6 inhibitors such as ketoconazole or quinidine.
Tiotropium was compared to ipratropium in three studies:

- Tiotropium (18 mcg daily) was compared to ipratropium (40 mcg QID) during long-term treatment of 288 patients with stable COPD in a 14-center, double-blind, double-dummy, parallel group 13 week study. Tiotropium showed superiority over ipratropium in trough, average and peak FEV\textsubscript{1} levels, trough and average FVC levels, and weekly mean morning and evening PEF. The use of concomitant albuterol was also lower in the tiotropium treated patients. Dry mouth was seen in 14.7% of tiotropium treated patients versus 10.3% of ipratropium treated patients.

- Two randomized, double-blind, double-dummy studies of one year in length evaluated tiotropium (18 mcg daily) or ipratropium (50 mcg QID). Mean baseline FEV\textsubscript{1} values were 41.9% of predicted value for tiotropium and 39.4% of predicted value for ipratropium. An improvement in trough FEV\textsubscript{1} at one year of 0.12 ± 0.01L was seen in the tiotropium group compared to a decline of 0.03 ± 0.02 L in the ipratropium group (p<0.001). Tiotropium increased time to first exacerbation (p=0.01), reduced the number of exacerbations of COPD by 24% (p<0.01) and increased the time to first hospitalization (p=0.05) compared to ipratropium. Adverse events were similar among the two groups; however, tiotropium caused slightly more dry mouth.

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend a stepwise approach for the treatment of COPD based on severity of disease. A SABA on a PRN basis should be used for mild COPD, and one or more long-acting bronchodilators on a regular basis should be used for moderate and severe COPD. The guidelines do not specify agents of choice. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend a similar stepwise approach for the treatment of COPD. These groups specifically state a PRN beta\textsubscript{2} agonist should be used for intermittent symptoms, and for persistent symptoms, regular use of either a long-acting bronchodilator or a short-acting bronchodilator QID plus a PRN beta\textsubscript{2} agonist should be used. If an adequate response is not achieved, an alternative class of bronchodilator, such as an inhaled anticholinergic, or combination therapy may be considered.

**RECOMMENDATION:**

Inhaled anticholinergic agents can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations and improve the health status of patients with COPD. While current clinical guidelines do not distinguish between products, head to head studies seem to indicate that the long acting agent tiotropium may produce better efficacy and safety compared to ipratropium. Therefore, to allow for prescriber choice, it is recommended that at least two agents, one of which should be tiotropium, be available.

**COMMITTEE VOTE:**

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATROVENT HFA \textsuperscript{®} QL (ipratropium)</td>
<td>ALBUTEROL/IPRATROPiom SOLUTION \textsuperscript{cc, ql} (Compares to DuoNeb)</td>
<td></td>
</tr>
<tr>
<td>COMBIVENT \textsuperscript{®} QL (albuterol/ipratropium)</td>
<td>DUONEB \textsuperscript{®} CC, QL (albuterol/ipratropium)</td>
<td></td>
</tr>
<tr>
<td>IPRATROPiom, solution (Compares to Atrovent\textsuperscript{®})</td>
<td>SPIRIVA \textsuperscript{®} QL (tiotropium)</td>
<td></td>
</tr>
</tbody>
</table>

**REREVIEW: INHALED ANTICHOLINERGICS**

**Clinical Criteria for albuterol/ipratropium and Duoneb\textsuperscript{®}**

For PA approval, there must be an adequate trial and failure of the individual components, albuterol and ipratropium nebulized solutions.
COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Quantity Limits

Albuterol/Ipratropium 180 nebs/month  
Atrovent HFA® 2 inhalers/month  
Combivent® 2 inhalers/month  
DuoNeb® 180 nebs/month  
Spiriva® 1/day

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


REVIEW: LEUKOTRIENE MODIFIERS

BACKGROUND

• There are two classes of agents in the leukotriene modifiers: leukotriene formation inhibitors (zileuton and zileuton extended-release) and leukotriene receptor antagonists (montelukast and zafirlukast). Zileuton and zileuton extended-release block the synthesis of leukotrienes by inhibiting 5-lipoxygenase. Montelukast and zafirlukast selectively inhibit the cysteinyl leukotriene receptor. Reductions in cysteinyl leukotrienes result in bronchodilation and a reduction in symptoms of asthma and allergic rhinitis.

• FDA-approved indications are as follows:
  o Montelukast is approved for the treatment of seasonal allergic rhinitis in adults and children ≥2 years, the treatment of perennial allergic rhinitis in adults and children ≥6 months, the prophylaxis and chronic management of asthma in adults and children ≥12 months and the prevention of exercise-induced bronchospasm (EIB) for patients ≥15 years.
  o Zafirlukast is approved for the prophylaxis and chronic management of asthma in adults and children 5 years and older.
  o Zileuton and zileuton extended-release are indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years and older.

• Common side effects are as follows:
  o Montelukast may cause otitis, pharyngitis, influenza, fever, sinusitis, cough, upper respiratory infection, headache and diarrhea.
  o Common side effects for zafirlukast include headache and abdominal pain.
  o Zileuton and zileuton ER are commonly associated with abdominal pain, dyspepsia, N/V, myalgia and elevated liver enzymes.
• Zileuton and Zileuton ER are contraindicated in patients with active liver disease. Zileuton ER is also contraindicated with ALT elevations ≥ 3 times the upper limit of normal.

• These agents are not indicated for reversal of bronchospasm during an acute asthma attack. Short-acting inhaled beta-agonists should be available for these situations.

• No published trials are available comparing the leukotriene modifiers head to head. Studies have been conducted comparing the leukotriene modifiers with other agents used for asthma and allergic rhinitis. These comparative studies do not provide conclusive evidence to suggest that one leukotriene modifier is more effective than the others.

• Leukotriene modifiers are beneficial in the treatment and prophylaxis of asthma. The following chart outlines the 2007 asthma guidelines from the NHLBI:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Birth to 4 years</th>
<th>Ages 5 to 11 years</th>
<th>Ages ≥ 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Intermittent</td>
<td>No daily meds needed PRN SABA</td>
<td>No daily meds needed PRN SABA</td>
<td>No daily meds needed PRN SABA</td>
</tr>
<tr>
<td>Step 2 Persistent</td>
<td>Low dose ICS Alternative: cromolyn or montelukast</td>
<td>Low dose ICS Alternative: cromolyn, leukotrien receptor antagonist (LTRA), nedocromil, or theophylline</td>
<td>Low dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline</td>
</tr>
<tr>
<td>Step 3 Persistent</td>
<td>Medium dose ICS</td>
<td>Low dose ICS AND LABA OR LTRA OR theophylline OR medium dose ICS</td>
<td>Low dose ICS AND LABA OR medium-dose ICS Alternatives: Low dose ICS AND either LTRA, theophylline or zileuton</td>
</tr>
<tr>
<td>Step 4 Persistent</td>
<td>Medium dose ICS AND LABA OR montelukast</td>
<td>Medium dose ICS AND LABA Alternative: medium dose ICS AND either LTRA or theophylline</td>
<td>Medium dose ICS AND LABA Alternative: medium dose ICS AND either LTRA, theophylline or zileuton</td>
</tr>
<tr>
<td>Step 5 Persistent</td>
<td>High dose ICS AND LABA OR montelukast Alternative: high dose ICS AND either LTRA or theophylline</td>
<td>High dose ICS AND LABA Alternative: high dose ICS AND either LTRA or theophylline</td>
<td>High dose ICS AND LABA Consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td>Step 6 Persistent</td>
<td>High dose ICS AND LABA AND oral steroids Alternative: high dose ICS AND either LTRA or theophylline PLUS oral steroids</td>
<td>High dose ICS AND LABA AND oral steroids</td>
<td>High dose ICS AND LABA AND oral steroids Consider omalizumab for patients who have allergies</td>
</tr>
</tbody>
</table>

• The 1998 AAAAI allergic rhinitis guidelines recommend that, for mild to moderate allergic rhinitis symptoms, either an oral second generation antihistamine or an intranasal corticosteroid be utilized. In patients who do not respond to monotherapy, combination therapy with an oral second generation antihistamine plus an intranasal corticosteroid may be helpful. While not specifically recommended in AAAAI allergic rhinitis guidelines, the leukotriene modifiers are useful in the treatment of allergic rhinitis for those patients who also have asthma or for those individuals who do not respond to treatment with oral antihistamines or nasal steroids.

**RECOMMENDATION:**
According to the NHLBI, inhaled corticosteroids are the cornerstone of treatment for asthma. Leukotriene modifiers should be considered as a potential alternative or add-on therapy for those patients with persistent asthma. Guidelines indicate that leukotriene modifiers can be used as controller medications in the treatment of asthma particularly for those ages four and under. For patients ages five and older, the preferred adjunctive therapy to inhaled corticosteroids is a long-acting inhaled beta agonist (rather than a leukotriene modifier). Leukotriene modifiers are beneficial in the treatment of AR, but should be considered second line medications after trial and failure of topical nasal steroids and minimally sedating antihistamines.
RESPIRATORY AGENTS

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: LEUKOTRIENE MODIFIERS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGULAIR® 31.4L   (montelukast)</td>
<td>ACCOLATE® 90L (zafirlukast)</td>
</tr>
<tr>
<td></td>
<td>ZYFLO® (zileuton)</td>
</tr>
<tr>
<td></td>
<td>ZYFLO® CR (zileuton controlled release)</td>
</tr>
</tbody>
</table>

Quantity Limits
- Accolate® 2 per day
- Singulair® 1 per day

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Step Therapy for Singulair®
- For the treatment of asthma in patients <21 years old, Singulair® will be approved, provided there is concomitant use of a short-acting beta₂ agonists.
- For treatment of asthma in patients ≥ 21 years old, Singulair® will be approved, provided there is concomitant use of at least a short-acting beta₂ agonist and an inhaled corticosteroid.
- For treatment of Seasonal Allergic Rhinitis in patients of any age, the patient must have failed an adequate trial of a non-sedating antihistamine and a nasal steroid prior to Singulair®.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References

NEW: ANTI-ASTHMA MONOCLONAL ANTIBODIES

BACKGROUND
- Asthma is a chronic airway disease caused by inflammation of the bronchial tubes. Many asthma patients are atopic and possess specific IgE antibodies to the allergens responsible for their asthma attacks.
- Omalizumab, the only monoclonal antibody used for asthma, inhibits the binding of IgE to the high-affinity IgE receptor (FceRI) on the surface of mast cells and basophils thereby limiting the release of the mediators of the allergic response. Omalizumab also reduces the number of FceRI receptors on basophils in atopic patients.
Omalizumab is FDA approved for the chronic treatment of moderate or severe persistent allergic asthma in patients who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with standard asthma therapy.

The most common adverse reactions associated with omalizumab are injection site reactions (45%, 12% severe), viral infections (23%), upper respiratory tract infections (20%), sinusitis (16%) and pharyngitis (11%). Other rare adverse reactions include malignant neoplasm (0.5%), anaphylaxis (0.1-0.2%) and thrombocytopenia.

- Omalizumab carries a black box warning regarding the risk of anaphylaxis. Patients should be closely observed following administration of the drug.
- The use of omalizumab in patients less than 12 years old or greater than 65 years old is cautioned due to limited outcomes data. Omalizumab is not to be used in the case of an acute asthma exacerbation, and concomitant steroid therapy should not be discontinued abruptly.

The efficacy of omalizumab was evaluated in 3 randomized, double-blind, placebo-controlled, multicenter trials involving 1317 patients. Patients were 12 to 76 years old with moderate to severe persistent asthma for at least 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta-agonists with or without a long acting beta agonist. Patients received omalizumab for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. ICS dosages were then reduced stepwise over the next 12-16 weeks. The number of exacerbations per patient was reduced in patients treated with omalizumab in two of the studies, while the number of exacerbations was similar to that of placebo-treated patients in one study. Hospitalization rates were not significantly different between omalizumab and placebo-treated patients. In all 3 of the studies, a reduction of asthma exacerbations was not observed in omalizumab-treated patients who had FEV$_1$ > 80% at the time of randomization or in patients who required oral steroids as maintenance therapy.

A meta-analysis was performed using six controlled clinical trials that evaluated the effects on quality of life using add-on omalizumab (n=1342) versus control (n=1206) in patients with severe persistent allergic asthma. Quality of life was assessed at baseline and at the end of therapy using the Juniper Asthma Quality of Life Questionnaire. Results showed a mean increase in quality of life score of 1.01 in the omalizumab group compared to 0.61 in the control group (p < 0.001). Additionally, 66.3% of omalizumab treated patients achieved a clinically meaningful improvement in quality of life versus 52.4% of the control group (p=0.001).

The 2007 NHLBI guidelines states that omalizumab may be used as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma which is inadequately controlled on a combination of an inhaled corticosteroid and a long-acting beta agonist.

**RECOMMENDATION:**
Omalizumab is used in allergic asthma because it limits the release of the mediators of the allergic response. Omalizumab has been shown to reduce asthma related symptoms and improve quality of life in patients with severe persistent allergic asthma. It is recommended that omalizumab be available for patients with moderate or severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with the combination of an inhaled corticosteroid and a long acting beta agonist.

**COMMITTEE VOTE:**

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

**NEW: ANTI-ASTHMA MONOCLONAL ANTIBODIES**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>XOLAIR® CC (omalizumab)</td>
</tr>
</tbody>
</table>
Clinical Criteria for Xolair® (omalizumab)

Omalizumab will be approved if ALL of the following criteria are met:

- Diagnosis of step 5 or higher (moderate to severe persistent) asthma; AND
- Inadequately controlled asthma despite therapy with an inhaled or oral corticosteroid; AND a long acting beta agonist (unless there is a documented intolerance or contraindication); AND
- Patient has a positive skin test or in vitro reactivity (RAST test) to a perennial aeroallergen

**NOTE: Safety and efficacy have not been established in children less than 12 years of age. Length of authorization: 6 months, subsequent renewals will be granted upon verification of marked clinical improvement.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


NEW: ANTI-VIRAL MONOCLONAL ANTIBODIES

BACKGROUND

- Respiratory Syncytial Virus (RSV) causes an upper respiratory tract infection similar to the common cold. RSV is self-limiting in otherwise healthy individuals, but it can cause serious complications in babies born prematurely who are less than 6 months of age during RSV season and in infants and children with comorbid conditions such as chronic lung disease (CLD), congenital heart disease (CHD) and immunodeficiency. The RSV season tends to occur October through April each year in Tennessee, and infants and children at increased risk for severe disease may require prophylactic treatment during the RSV season.
- Palivizumab, the only prophylactic medication against RSV, neutralizes RSV and inhibits its fusion activity. This results in the inhibition of RSV replication.
- Palivizumab is indicated for prophylaxis against severe lower respiratory tract disease caused by RSV in high-risk pediatric patients.
- The most common adverse reactions seen in palivizumab-treated patients are injection site reactions, cough, GI upset, fever, rash, rhinitis, upper respiratory tract infection and wheezing. Anaphylaxis is rare (< 1 case per 100,000 patients).
  - Clinicians should be warned to use palivizumab with caution in patients with thrombocytopenia or coagulation disorders as it is an IM injection. In addition, palivizumab is not indicated for the treatment of RSV infections.
- Two randomized, double-blind, placebo-controlled trials examined the safety and efficacy of palivizumab for prophylaxis against RSV infection in pediatric patients at high risk for an RSV-related hospitalization.
One trial was conducted during a single RSV season and included 1,502 patients. Patients were either ≤ 24 months of age with CLD or ≤ 6 months of age and born at ≤ 35 weeks’ gestation. Patients were given 15 mg/kg of palivizumab versus placebo IM monthly for 5 injections and were followed for 30 days after the last injection. Monthly prophylaxis with palivizumab was associated with a 55% reduction in hospitalization as a result of RSV (p=0.00004). Significant reductions were observed in both children with CLD (p=0.038) and premature children without CLD (p=<0.001). Palivizumab did not decrease the severity of disease among hospitalized patients.

The second trial was conducted over 4 consecutive seasons and included 1,287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease (CHD). Participants received palivizumab 15 mg/kg or an equivalent volume of placebo IM monthly for 5 injections and were followed for 150 days from randomization. Hospitalization rates were 5.3% in patients with CHD treated with palivizumab versus 9.7% in controls (p=0.003). Palivizumab did not decrease the severity of disease among hospitalized patients.

The American Academy of Pediatrics (AAP) states that prophylaxis using palivizumab or Respiratory Syncytial Virus Globulin Intravenous (RSV-IVIG) should be considered for infants and children younger than 2 years with CLD who have required medical therapy for CLD within 6 months prior to the start of RSV season. The AAP prefers palivizumab over RSV-IVIG because of its ease of administration, safety and efficacy. The AAP further states that patients with more severe CLD may benefit from prophylaxis with palivizumab during a second RSV season if they continue to require medical therapy for pulmonary or cardiac dysfunction. The guidelines further state that infants born at ≤32 weeks’ gestation may benefit from RSV prophylaxis even if they do not have CLD. Infants born at ≤ 28 weeks may benefit from prophylaxis during their first RSV season up to 12 months of age, and infants born at 29-32 weeks gestation may benefit from prophylaxis up to 6 months of age. For infants born between 32 and 35 weeks gestation, prophylaxis should be reserved for infants who are younger than 6 months and have at least two risk factors for RSV, such as day care enrollment, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways or severe neuromuscular disease. Children ≤ 24 months with hemodynamically significant cyanotic and acyanotic CHD will benefit from prophylaxis with palivizumab if they are receiving medication to control CHF, have moderate to severe pulmonary hypertension or have cyanotic heart disease.

**RECOMMENDATION:**
Palivizumab is effective as a preventative therapy against severe viral lower respiratory tract infection in pediatric patients at high risk for RSV. The AAP has very specific recommendations about the patient population that has been shown to benefit from palivizumab therapy. Therefore, it is recommended that palivizumab be available for use during RSV season in patients who meet the high-risk criteria set forward by the AAP.

**COMMITTEE VOTE:**
APPROVED DISAPPROVED APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>SYNAGIS® (palivizumab)</td>
</tr>
</tbody>
</table>
Clinical Criteria for Synagis®

Synagis® may be approved for patients under the age of 2 years meeting the following criteria:

- For patients < 6 months of age at the onset of the RSV season:
  - If patient was born at 32 weeks gestation or earlier- May approve therapy beginning October 1st with a last date of therapy not after the end of the RSV season (April 30th).
  - If the patient was born between 33-35 weeks gestation, the patient must have **two or more** of the following risk factors for severe RSV disease:
    - Exposure to environmental air pollutants, including tobacco smoke
    - Child care out of the home (> 4 hours per week)
    - Siblings attending school or day-care
    - Congenital abnormalities of the airways
    - Severe neuromuscular disease
    - Long distance from hospital care, defined as 30 miles or 30 minutes
    - Low birth weight (<2500 gm)

- For patients <12 months of age at the onset of the RSV season AND born at 28 weeks gestation or earlier- May approve therapy beginning October 1st with a last date of therapy not after the end of the RSV season (April 30th). For patients <12 months of age at the onset of the RSV season AND born at 28 weeks gestation or earlier- May approve therapy beginning October 1st with a last date of therapy not after the end of the RSV season (April 30th).

- For patients <24 months of age at the onset of the RSV season:
  - If the patient has Chronic Lung Disease (formerly called bronchopulmonary dysplasia) that has required daily respiratory medications or treatments within the previous 6 months, may approve therapy beginning October 1st with a last date of therapy not after the end of the RSV season (April 30th).
  - If the patient has a diagnosis of hemodynamically significant congenital heart disease (those receiving medication to control CHF, with moderate to severe pulmonary hypertension or with cyanotic heart disease), may approve therapy beginning October 1st with a last date of therapy not after the end of the RSV season (April 30).

Of note, Synagis will **not** be approved for those infants and children with hemodynamically insignificant heart disease including:
- Secundum atrial septal defects
- Small ventricular septal defect
- Pulmonic stenosis
- Uncomplicated aortic stenosis
- Mild coarctation of the aorta
- Patent ductus arteriosus
- Mild cardiomyopathy in patients who are not receiving medical therapy
- Heart lesions adequately corrected by surgery, unless the patient continues to require medication for CHF

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED   APPROVED with MODIFICATION
References

LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

*Acceptable reasons include:*
- **Allergy** to medications not requiring prior approval
- **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
- **History** of unacceptable/toxic side effects to medications not requiring prior approval

The requested medication may be approved if both of the following are true:
- If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
- The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

The requested medication may be approved if the following is true:
- An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

-------------------------------------------------------------------------------------------------

The information provided for each drug class within the Central Nervous System Agents is organized into the following sections when applicable:

**BACKGROUND:**
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

**RECOMMENDATION:**
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
**BACKGROUND**

- Antihyperkinesis agents are most commonly used in the treatment of attention-deficit/hyperactivity disorder (ADHD). ADHD is characterized by the symptoms of inattention, hyperactivity, and impulsivity which may be due to dopamine and/or norepinephrine dysfunction in areas of the cerebral cortex. These agents can also be used to treat disorders of hypersomnolence, including narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSA/HS), and shift work sleep disorder (SWSD).

- Though the exact mechanism of action is not known, it is thought that the sympathomimetic stimulants act by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. Amphetamines appear to release newly synthesized dopamine while methylphenidate causes the release of stored dopamine. Atomoxetine, a non-stimulant, is a selective inhibitor of the presynaptic norepinephrine transporter, resulting in increased norepinephrine and dopamine levels.

- Though pharmacologically different from the sympathomimetic agents, modafinil also causes wake-promoting effects through CNS activation. CNS-activation with modafinil occurs in discrete brain regions, suggesting a more specific wake-promoting effect, though the mechanism of action is uncertain.

- FDA-Approved Indications:

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADHD (age 3-5yrs)</th>
<th>ADHD (age ≥ 6 yrs)</th>
<th>Narcolepsy (age ≥ 6 yrs)</th>
<th>Excessive Sleepiness associated with narcolepsy, OSA/HS &amp; SWSD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dextroamphetamine IR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>dextroamphetamine ER</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>methamphetamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed amphetamine salts IR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>mixed amphetamine salts ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methylphenidate IR</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>methylphenidate SR</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>methylphenidate ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methylphenidate transdermal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamethylphenidate IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamethylphenidate ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-stimulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**FDA-Approved Indications:**

- ADHD (age 3-5yrs)
- ADHD (age ≥ 6 yrs)
- Narcolepsy (age ≥ 6 yrs)
- Excessive Sleepiness associated with narcolepsy, OSA/HS & SWSD
Adverse events associated with the stimulant medications are generally considered mild to moderate and are dose-dependent. The most common adverse events associated with stimulant use are appetite decrease, weight loss, insomnia, headache, stomachache, nervousness, and social withdrawal. Most of these effects can be managed by dose adjustment, timing of administration, or switching to an alternate stimulant agent. Growth delay is a common concern; however, the American Academy of Pediatrics (AAP) released a policy stating that there is “no significant impairment of height attained” in adult life. Growth delay may be a concern in mid-adolescence but appears to normalize in late adolescence with any decrease in growth early in treatment compensated for later. Stimulants can increase the occurrence of new onset motor tics, as well as exacerbate existing tics. In general, there are no statistically significant differences in the incidences of adverse events either between immediate-release and modified-release formulations, or between dextroamphetamine and methylphenidate.

Common adverse events associated with atomoxetine include: increased blood pressure, tachycardia, decreased appetite, upper abdominal pain, weight loss, and headache. Rare, but serious, adverse events include: liver injury, seizures, and suicidal ideations (in pediatric population). Serious or life-threatening rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with modafinil.

- Amphetamines and methylphenidate products carry a black box warning regarding their high potential for abuse and drug dependence. In 2006, the FDA mandated adding an additional black box warning to these products about the risk of sudden death and serious cardiovascular events associated with misuse.
- Methylphenidate products carry a warning that careful supervision is required during drug withdrawal due to potential development of depression and/or unmasking of symptoms of underlying disorder.
- Atomoxetine carries a black box warning about the increased risk of suicidal ideation in children or adolescents. Suicidal ideation occurred in 0.4% of patients and all occurrences were within the first month of treatment. Patients should be monitored closely during initiation of treatment with atomoxetine.
- In 2004, the FDA required atomoxetine to add a warning about severe liver injury based on reports of two patients who developed severe liver disease.

The stimulants, as well as atomoxetine, are contraindicated within 14 days following administration of MAO inhibitors as hypertensive crisis may occur with concurrent use. These agents are also contraindicated in patient with glaucoma. All stimulant agents are contraindicated in agitated patients.

Amphetamines are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, history of drug dependence, moderate to severe hypertension, or hyperthyroidism.

Methylphenidate and dexamfetamine are contraindicated in patients with motor tics, anxiety, Tourette’s syndrome or family history of Tourette’s syndrome.

- Amphetamines, methylphenidate, and dexamfetamine products should be used with caution in patients with:
  - Bipolar disorder, as the condition may be exacerbated by stimulant use
  - Cardiovascular conditions which may be compromised by increases in blood pressure or heart rate
  - Seizures, as stimulant use may lower the seizure threshold
  - Serious structural cardiac abnormalities as sudden death has been associated with CNS stimulant use in these patients
o Atomoxetine should be used with caution in patients with:
  ▪ Bipolar disorder, as mixed/manic episode may be induced
  ▪ Cardiovascular disease, cerebrovascular disease, hypertension, tachycardia due to risk of increased blood pressure and heart rate
  ▪ Orthostatic hypotension
  ▪ Structural cardiac abnormalities, cardiomyopathy, cardiac arrhythmias or coronary artery disease due to risk of sudden death at usual doses
  ▪ Moderate hepatic insufficiency, doses of atomoxetine should be reduced by 50 percent

o Modafinil should be used with caution in patients with:
  ▪ Depression, mania, psychosis or suicidal ideation due to increased risk of psychiatric adverse effects
  ▪ Elderly patients as drug clearance may be reduced
  ▪ Hepatic impairment as drug clearance may be reduced
  ▪ Left ventricular hypertrophy due to increased risk of cardiac adverse events
  ▪ Moderate hepatic insufficiency, doses of modafinil should be reduced by 50 percent
  ▪ Severe renal impairment due to a nine-fold increase in bioavailability of inactive metabolite, modafinil acid

- Onset of action and duration of action vary between products, in large part due to immediate release vs. extended release formulations. Dosing intervals are dependent on formulation. Once-daily dosing, or extended release formulations may be preferred in some settings (i.e. compliance, school settings) due to potential difficulties with multiple daily dosing.

- Drug-Drug Interactions:
  o CNS effects can be additive with use of any of the antihyperkinesis agents concomitantly with other psychostimulants or with sympathomimetics; therefore, these combinations should be avoided.
  o Concomitant use of amphetamines with other serotonergic agents should be avoided due to the potential for serotonin syndrome that may be associated with the increased release of serotonin in the CNS.
  o Lithium, haloperidol and chlorpromazine may antagonize the central stimulating effects of amphetamines.
  o Coadministration of modafinil and combination contraceptives has reduced the contraceptive bioavailability and potentially reduced contraceptive effectiveness.

- Numerous head to head trials have been conducted regarding the use of stimulant medications in the treatment of ADHD. Trials and meta-analyses to date have not shown any clear advantage of one stimulant medication over another or among dosage forms of any given agent. The AAP states that all of the stimulants are equally effective for this indication.
  o A placebo-controlled, double blind study conducted in 516 children ages 6-16 with ADHD compared atomoxetine to methylphenidate during acute treatment for six weeks. Response occurred in 56% of methylphenidate patients compared to 45% of atomoxetine patients (p=0.016).
  o A meta-analysis of 29 randomized, double-blind, placebo-controlled studies, which involved over 4400 children with ADHD, showed that stimulant medications are significantly more effective than non-stimulant ADHD medications in the treatment of ADHD.
  o No head to head trials have been conducted comparing modafinil to traditional stimulant agents for use in narcolepsy.
• The AAP recommends stimulants as first line treatment for ADHD, though no differentiation is made between the available agents, formulations, or dosage forms. Atomoxetine may be considered as an alternative to first line therapy for patients with an active substance abuse problem where there may be concerns about using a controlled substance.

• The European Federation of Neurological Societies (EFNS) recommends that first-line pharmacological treatment of excessive daytime sleepiness should rely on modafinil, with methylphenidate as a second-line option due to its potential for abuse.

• The American Academy of Sleep (AASM) practice parameters for narcolepsy states that treatment options for daytime sleepiness from narcolepsy include modafinil, amphetamine, methamphetamine, dextroamphetamine, and methylphenidate. While the guidelines point out that the amphetamines are most likely to be associated with tolerance, they do not recommend any particular treatment option over the others.

RECOMMENDATION:
The stimulants and atomoxetine are approved for the treatment of ADHD, while the stimulants are also approved for the treatment of narcolepsy. Current treatment guidelines from the AAP place stimulants as first line therapy for ADHD. Although FDA-approved indications vary regarding age of treatment, all of the stimulants have similar efficacy and adverse event rates, and current guidelines make no differentiation between the available agents, formulations, or dosage forms. Therefore, all of the stimulants can be considered therapeutic alternatives to one another, though extended release agents may be preferred in some settings due to difficulties with multiple daily dosing. As stated in the AAP guidelines, it is reasonable to switch to another stimulant agent if there is an inadequate response or intolerable adverse reaction to a single agent. In order to allow for patient and prescriber preference, it is recommended that at least two distinct stimulant agents be available, one of which should be an extended release formulation. Based on available clinical trials, atomoxetine can be considered a second line agent behind the stimulants for the treatment of ADHD; however, given its low abuse potential, atomoxetine has utility in cases of suspected drug abuse; therefore, its use should be reserved for these instances.

For the treatment of narcolepsy, modafinil, amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are all reasonable treatment alternatives. The current literature indicates that modafinil may be better tolerated than traditional stimulants for the treatment of excessive daytime sleepiness. In addition, the EFNS recommends modafinil as first line therapy for narcolepsy. Therefore, modafinil should be available for use in hypersomnia with clinical criteria to restrict its use to approved indications only.

COMMITTEE VOTE:
APPROVED        DISAPPROVED        APPROVED with MODIFICATION
## REREVIEW: ANTIHYPERKINESIS AGENTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDERALL® XR QL (amphetamine salt combination)</td>
<td>ADDERALL® (amphetamine salt combination)</td>
</tr>
<tr>
<td>AMPHETAMINE SALT COMBINATION (compares to Adderall®)</td>
<td>DAYTRANA® QL (methylphenidate)</td>
</tr>
<tr>
<td>CONCERTA® QL (methylphenidate)</td>
<td>DESOXYN® (methamphetamine)</td>
</tr>
<tr>
<td>DEXAMPHETAMINE (compares to Dexedrine®, Dextrostat®, Dexedrine Spansules®)</td>
<td>DEXEDRINE® (dextroamphetamine)</td>
</tr>
<tr>
<td>DEXEDRINE® SPANSULE (dextroamphetamine)</td>
<td>DEXEDRINE® SPANSULE (dextroamphetamine)</td>
</tr>
<tr>
<td>METHAMPHETAMINE (compares to Desoxyn®)</td>
<td>FOCALIN® (dexamphetamine)</td>
</tr>
<tr>
<td>METHYLPHENIDATE (compares to Methylin®, Ritalin®)</td>
<td>METHYLPHENIDATE (methylphenidate tablets only)</td>
</tr>
<tr>
<td>METHYLPHENIDATE ER (compares to Metadate® ER, Methylin® ER, Ritalin® SR)</td>
<td>PROVIGIL® CC, QL (modafinil)</td>
</tr>
<tr>
<td>FOCALIN® XR QL (dexamphetamine)</td>
<td>RITALIN® (methylphenidate)</td>
</tr>
<tr>
<td>METADATE® CD QL (methylphenidate)</td>
<td>RITALIN® LA QL (methylphenidate)</td>
</tr>
<tr>
<td>METADATE® ER QL (methylphenidate)</td>
<td>RITALIN® SR (methylphenidate)</td>
</tr>
<tr>
<td>METHAMPHETAMINE (compares to Desoxyn®)</td>
<td>STRATTERA® CC (atomoxetine)</td>
</tr>
<tr>
<td>METHYLPHENIDATE (methylphenidate chewable tabs and solution only)</td>
<td>VYVANSE® QL (lisdexamfetamine)</td>
</tr>
<tr>
<td>METHYLPHENIDATE (methylphenidate tablets only)</td>
<td></td>
</tr>
<tr>
<td>ADDERALL® (amphetamine salt combination)</td>
<td></td>
</tr>
<tr>
<td>DAYTRANA® QL (methylphenidate)</td>
<td></td>
</tr>
<tr>
<td>DESOXYN® (methamphetamine)</td>
<td></td>
</tr>
<tr>
<td>DEXEDRINE® (dextroamphetamine)</td>
<td></td>
</tr>
<tr>
<td>DEXEDRINE® SPANSULE (dextroamphetamine)</td>
<td></td>
</tr>
<tr>
<td>FOCALIN® (dexamphetamine)</td>
<td></td>
</tr>
<tr>
<td>METHYLPHENIDATE (methylphenidate tablets only)</td>
<td></td>
</tr>
<tr>
<td>PROVIGIL® CC, QL (modafinil)</td>
<td></td>
</tr>
<tr>
<td>RITALIN® (methylphenidate)</td>
<td></td>
</tr>
<tr>
<td>RITALIN® LA QL (methylphenidate)</td>
<td></td>
</tr>
<tr>
<td>RITALIN® SR (methylphenidate)</td>
<td></td>
</tr>
<tr>
<td>STRATTERA® CC (atomoxetine)</td>
<td></td>
</tr>
<tr>
<td>VYVANSE® QL (lisdexamfetamine)</td>
<td></td>
</tr>
</tbody>
</table>

### Quantity Limits

- **Adderall® XR**: 5, 10, 15 mg tabs: 1/day
  - 20, 25, 30 mg tabs: 2/day
- **Concerta®**: 1/day
- **Daytrana®**: 10, 15, 20, 30 mg patch 1/day
- **Focalin® XR**: 1/day
- **Metadate® CD**: 10, 20, 30, 40, 50, 60 mg tabs 1/day
- **Metadate® ER**: 10 mg tabs 1/day
  - 20 mg tabs 3/day
- **Provigil®**: 2/day
- **Ritalin® LA**: 1/day
- **Vyvanse®**: 1/day

### COMMITTEE VOTE:

- **APPROVED**
- **DISAPPROVED**
- **APPROVED with MODIFICATION**

### Clinical Criteria for Provigil®

Diagnoses for which Provigil® will be approved include:

- Obstructive sleep apnea/hypopnea syndrome
- Shift work sleep disorder
- Narcolepsy
- ADD/ADHD: Must have had a failure of 2 preferred agents or a contraindication to stimulant therapy for this indication

### COMMITTEE VOTE:

- **APPROVED**
- **DISAPPROVED**
- **APPROVED with MODIFICATION**
CENTRAL NERVOUS SYSTEM AGENTS

Clinical Criteria for Strattera®

Strattera® will only be approved for a diagnosis of ADD/ADHD. If there is a question of substance abuse with the patient, patient’s family, or with use while in college, no failure of a stimulant is required to receive Strattera®.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

References


REREVIEW: ANTI-MIGRAINE: 5-HT1 RECEPTOR AGONISTS

BACKGROUND

- Migraines result from activity within the trigeminovascular system causing a release of vasoactive neuropeptides, vasodilation, dural plasma extravasation and perivascular inflammation.

- It is sometimes difficult to distinguish migraine headache from tension-type headache; however, migraines are usually episodic, lasting from 4-72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravation of pain upon moving, pain of moderate to severe intensity accompanied by nausea, vomiting, photophobia or phonophobia. Acetaminophen, NSAIDs, ergot alkaloids, and 5-HT1 receptor agonists or “triptans” can all be used to treat migraines.

- Triptans stimulate vascular 5-HT1B receptors resulting in intracranial vessel constriction, presynaptic 5-HT1D receptors resulting in inhibition of vasoactive neuropeptide release and 5-HT1D receptors within the brainstem causing interruption of pain signal transmission.

- All triptans are FDA approved for the acute treatment of migraine attacks with or without aura in adults. Injectable sumatriptan is also indicated for the acute treatment of cluster headaches in adults. Triptans are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

- The most common adverse events seen in triptan users are dizziness, nausea, somnolence, flushing, palpitations, pain and pressure sensations and paresthesia. The nasal sprays commonly cause unusual taste and nasal irritation.
Triptans are contraindicated in patients with ischemic heart disease or patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm or other significant underlying cardiovascular disease. Naratriptan is also contraindicated in patients with severe renal impairment (CrCl <15 mL/min) and severe hepatic impairment (Child-Pugh grade C).

As triptans may cause coronary vasospasm; these agents should be used cautiously in patients with coronary artery disease or cerebrovascular event. The FDA cautioned that serotonin syndrome could occur if triptans are used with SSRIs or SNRIs as well. All triptans are pregnancy category C.

Triptans should not be given within 24 hours of ergot alkaloids or other triptans because this combination may cause prolonged vasospastic reactions. Monoamine oxidase inhibitors should be avoided for 2 weeks after administration of rizatriptan, sumatriptan or zolmitriptan. Eletriptan should be avoided within 72 hours of CYP450 3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, clarithromycin, ritonivir or nelfinavir due to possible elevation in serum levels of eletriptan. When administered concomitantly with propranolol, rizatriptan doses should not exceed 5 mg in any 24 hour period.

Frovatriptan has the longest half-life; therefore, it is conceivable that patients will not need to redose as frequently. However, there is no evidence that a second dose of frovatriptan is effective in patients who do not respond to a first dose.

- Multiple head-to-head trials have been conducted using the triptans.
  - One trial compared naratriptan to sumatriptan and found them to have similar efficacy.
  - Three trials compared zolmitriptan use to sumatriptan. Two studies showed similar efficacy, while one found zolmitriptan to be superior to sumatriptan.
  - Four trials compared eletriptan use to other triptans (2 compared it to sumatriptan, 1 to naratriptan, and 1 to zolmitriptan). Eletriptan was found to exhibit better efficacy than sumatriptan and naratriptan, and similar efficacy to zolmitriptan.
  - Four trials compared almotriptan to sumatriptan. All concluded that the products had similar efficacy; however, 3 found that almotriptan was associated with fewer side effects than sumatriptan.
  - Three trials compared rizatriptan use to other triptans (2 compared it to sumatriptan, 1 to naratriptan, and 1 to zolmitriptan). The studies found rizatriptan to have superior efficacy compared to naratriptan, similar efficacy but a faster onset of action compared to sumatriptan, and similar efficacy to zolmitriptan.

- The US Headache Consortium, the American Academy of Family Physicians, and the American College of Physicians-American Society of Internal Medicine recommend NSAIDs as first-line therapy for patients with mild to moderate migraine pain. Triptans and dihydroergotammines should be used for migraines that do not respond to NSAIDs. They further recommend a non-oral route of administration when nausea or vomiting is particularly troublesome early in the migraine. These groups recognize that naratriptan has a slightly delayed onset of pain relief, but they do not recommend any specific triptan over another. They also state that it is reasonable to switch to another triptan if there is an inadequate pain response or intolerable adverse reaction. Frovatriptan and eletriptan were not available when these guidelines were published.

**RECOMMENDATION:**
Triptans are approved for the acute treatment of migraine attacks with or without aura in adults, and they are recommended as possible alternatives to NSAIDs. Although available data shows mixed results, and the onset of action may vary slightly among agents, all of the triptans have similar efficacy and safety. However, it is reasonable to switch to another triptan if there is an inadequate pain response or intolerable adverse reaction to a single agent. Therefore, it is recommended that at least two distinct triptans be available. In order to ensure patient and provider choice, it is recommended that at least one non-oral dosage form be available for patients with migraines associated with nausea.
COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

REREVIEW: ANTI-MIGRAINE: 5-HT₁ RECEPTOR AGONISTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAXALT® QL (rizatriptan)</td>
<td>AMERGE® QL (naratriptan)</td>
</tr>
<tr>
<td>MAXALT MLT® QL (rizatriptan)</td>
<td>AXERT® QL (almotriptan)</td>
</tr>
<tr>
<td>ZOMIG® QL (zolmitriptan)</td>
<td>FROVA® QL (frovatriptan)</td>
</tr>
<tr>
<td>ZOMIG NASAL SPRAY® QL (zolmitriptan)</td>
<td>IMITREX® QL (sumatriptan)</td>
</tr>
<tr>
<td>ZOMIG ZMT® QL (Zolmitriptan)</td>
<td>IMITREX KIT/CARTRIDGE® QL (sumatriptan)</td>
</tr>
<tr>
<td>IMITREX® QL VIAL (sumatriptan)</td>
<td>IMITREX® QL NASAL(sumatriptan)</td>
</tr>
<tr>
<td></td>
<td>RELPAX® QL (eletriptan)</td>
</tr>
</tbody>
</table>

Quantity Limits

Amerge 9/month
Axert 12/month
Frova 9/month
Imitrex 9/month
Imitrex Vial 0.5 mL 4/month
Imitrex Kit/Cartridge 4/month
Imitrex Nasal 6/month
Maxalt 12/month
Maxalt MLT 12/month
Relpax 6/month
Zomig 6/month
Zomig Nasal Spray 6/month
Zomig ZMT 6/month

COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

References

BACKGROUND

- Although the exact etiology of depressive disorders is unknown, many theories focus on changes in neurotransmitter levels, including abnormal regulation of cholinergic, noradrenergic, dopaminergic, and serotonergic neurotransmission. Serotonin and norepinephrine are also involved in pain modulation in the brain and spinal cord.

- The mechanism of action of the SNRIs is believed to be related to their potentiation of both serotonergic and noradrenergic activity in the CNS, though the exact mechanism is unknown.

- All SNRIs are FDA-approved for the treatment of generalized anxiety disorder and major depressive disorder (MDD). Duloxetine is also approved for the management of diabetic peripheral neuropathy pain (DPNP). Venlafaxine carries an additional FDA-approved indication for the treatment of social anxiety disorder.

- Adverse events commonly associated with the use of SNRIs include: nausea, constipation, decreased appetite, headache, dizziness, fatigue, somnolence and dry mouth. Adverse events that are less common, but may pose serious risks include: orthostatic hypotension, syncope, hypertension, cardiac arrhythmias, and elevation of serum transaminases.

- There have been spontaneous reports of adverse reactions occurring upon discontinuation of the SNRIs, particularly when abruptly discontinued. These adverse reactions included the following: agitation, anxiety, confusion, dizziness, dysphoric mood, emotional instability, headache, hypomania, insomnia, irritability, lethargy, seizures, sensory disturbances, and tinnitus. Although these reactions are generally self-limiting, some have been reported to be severe. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

  - All antidepressants carry the following black box warning: “Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.”

  - Duloxetine is contraindicated in uncontrolled narrow-angle glaucoma due to increased risk of mydriasis.

  - Cautions:
    - All SNRIs are Pregnancy Category C.
    - Due to risk of hypertension with SNRIs, caution should be used in patients with uncontrolled hypertension.
    - Duloxetine is not recommended for use in patients with CrCl <30 ml/min or for patients with any degree of hepatic impairment.
    - Dose reductions of venlafaxine may be required in patients with renal or hepatic impairment.

  - Drug Interactions:
    - SNRIs are contraindicated with concomitant use of monoamine oxidase inhibitors due to the risk of potentially life-threatening serotonin syndrome.
    - SNRIs undergo metabolism in the liver via the cytochrome P450 enzyme system and are therefore subject to drug-drug interactions with other drugs metabolized by the same isoenzymes.

- Although no head-to-head trials have been conducted, several meta-analyses have been conducted to indirectly compare duloxetine and venlafaxine for the treatment of MDD.
Data obtained from 8 trials and over 1,700 patients were evaluated to compare efficacy and safety of duloxetine and venlafaxine XR in the treatment of MDD. There was a trend in favor of venlafaxine XR in regards to efficacy; however, the differences did not reach statistical significance. Reported adverse events were comparable between the drugs.

Another meta-analysis evaluated 17 trials for safety and efficacy of duloxetine and venlafaxine for the treatment of MDD. The results showed a statistically significant difference between treatments, with venlafaxine superior to duloxetine in treatment efficacy and response rates.

In the absence of head-to-head trial data, results from meta-analyses suggest that venlafaxine is superior to duloxetine for the treatment of major depressive disorder.

- There are currently no published head-to-head trials comparing duloxetine to other agents for the management of DPNP.
- SNRIs are claimed to be at least as effective as tricyclic antidepressants (TCAs) in the treatment of depression but with lower toxicity, and more efficacious than selective serotonin reuptake inhibitors (SSRIs).
  - The current American Psychiatric Association (APA) practice guidelines for the treatment of patients with MDD state “the effectiveness of antidepressant medications is generally comparable between classes” with selection based on adverse events and patient preference; however, these guidelines have not been updated since 2000, prior to the release of duloxetine.
  - The National Institute for Health and Clinical Excellence (NICE) guidelines for management of depression, updated in April 2007, recommend SSRIs as first line therapy for the treatment of depression, with SNRIs and TCAs as second line therapy. The primary role of SNRIs is as an alternative in patients with MDD who have responded poorly to other agents.

- Guidelines for the treatment of anxiety disorders also consider SNRIs to be second line therapy behind the SSRIs.
  - The 2007 guidelines from the American Academy of Child and Adolescent Psychiatry recommend SSRIs as first-line agents for the treatment of childhood anxiety disorders. Noradrenergic antidepressants, such as SNRIs and TCAs, may be considered alternatives to SSRIs, although their safety in children has not been as well-established as with the SSRIs.
  - The 2004 NICE guidelines for the management of anxiety disorders recommend SSRIs as first line, and if not effective after a 12-week course, then a TCA or other antidepressant (including venlafaxine) may be considered.

- Consensus guidelines for the treatment of DPNP from the Journal of Family Practice and the Mayo Clinic place duloxetine as a first-tier agent, along with pregabalin and TCAs. Duloxetine and pregabalin are the only agents FDA-approved for the treatment of DPNP.
RECOMMENDATION
The SNRIs, duloxetine and venlafaxine, are FDA-approved for the treatment of generalized anxiety disorder and MDD. Duloxetine is also approved for the management of DPNP. Venlafaxine carries an additional FDA-approved indication for the treatment of social anxiety disorder. Current NICE guidelines for the management of depression recommend SSRIs as first line therapy for the treatment of depression, with SNRIs and TCAs as second line therapy. The primary role of SNRIs is as an alternative in patients with MDD who have responded poorly to other agents. For the treatment of anxiety disorders, current guidelines recommend SSRIs as first line therapy, with the SNRIs and TCAs as second line options. Due to the lack of comparative trials and mixed results from meta-analyses, it is unclear whether any significant clinical differences exist between the available SNRIs for the treatment of MDD or anxiety disorders. However, the guidelines do not distinguish between the available SNRIs for either of these indications. For the treatment of DPNP, current guidelines place duloxetine as a first-tier agent.

Based on this information, venlafaxine and duloxetine can be considered therapeutic alternatives to one another for the treatment of MDD and anxiety disorders. It is recommended at least one SNRI be available with step therapy to restrict its use to patients who have responded poorly to SSRIs. Additionally, it is recommended that duloxetine be available for use in the treatment of DPNP.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

REREVIEW: SNRIs

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENLAFAXINE®ST,QL (compares to Effexor®)</td>
<td>CYMBALTA®ST,QL (duloxetine)</td>
</tr>
<tr>
<td>EFFEXOR XR®ST,QL (venlafaxine)</td>
<td>EFFEXOR®ST,QL (venlafaxine)</td>
</tr>
</tbody>
</table>

Quantity Limits
- Cymbalta® 20 & 30 mg: 2/day
  60 mg: 1/day
- Effexor® 2/day
- Effexor XR® 37.5 & 75 mg: 1/day
  150 mg: 2/day
- Venlafaxine: 2/day

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Class Step Therapy
SNRIs will only be authorized if the recipient has tried and failed a therapeutic course of SSRI at an appropriate dose (Defined as: 3 weeks at maximum tolerated dose within the recommended therapeutic range). If approved, then venlafaxine or Effexor XR® is the preferred agent.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Clinical Criteria for Cymbalta®:
Cymbalta® will be authorized for a diagnosis of diabetic peripheral neuropathic pain without trial and failure of an SSRI or any preferred agents within the SNRI class.
COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

References

LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most prescriptions for medications in this class would expire in 6 months, and thus would be approved for 6 months at a time.)

Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

Acceptable reasons include:

- **Allergy** to medications not requiring prior approval
- **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
- **History** of unacceptable/toxic side effects to medications not requiring prior approval

The requested medication may be approved if both of the following are true:

- If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
- The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

The requested medication may be approved if the following is true:

- An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class within the Analgesic Agents is organized into the following sections when applicable:

**BACKGROUND:**

- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

**RECOMMENDATION:**

- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
BACKGROUND

- The pathophysiology of pain involves a complex series of afferent and efferent neuronal connections that have not been fully explained. There are many kinds of pain which respond to different pharmacological therapies. Acute pain usually requires only temporary therapy and is best treated with NSAIDs, non-narcotic analgesics or short-acting opioids. For chronic pain, non-narcotic preparations should be used when possible. Anticonvulsants and antidepressants are more useful than narcotics for neuropathic pain. Occasionally pain is refractory to conventional therapy and nonpharmacologic modalities such as nerve blocks, acupuncture, and massage and relaxation therapy may be appropriate.

- Long-acting narcotics produce their physiological effects by interacting with the opioid mu-receptors located in the brain, spinal cord, and smooth muscle. These agents also produce respiratory depression by direct action on the respiratory center located in the brain stem.

- Fentanyl is indicated for the treatment of chronic pain in patients who require continuous opioid analgesia and the pain cannot be managed by lesser means such as NSAIDs, opioid combination products or immediate release opioids. Methadone is FDA approved for the relief of moderate to severe pain and detoxification and maintenance treatment of narcotic addiction. Extended release preparations of morphine and oxymorphone are indicated for the treatment of moderate to severe pain requiring around-the-clock, continuous opioid for an extended time. Oramorph<sup>®</sup> SR is specifically indicated for the relief of pain in patients who require opioids for more than a few days.

- The most common adverse reactions caused by the long-acting narcotics include: asthenia, constipation, dizziness, dyspnea, headache, nausea, rash, somnolence and vomiting. Parenteral use of MS Contin<sup>®</sup> may cause tissue necrosis, infection, pulmonary granulomas and increased risk of endocarditis and valvular heart injury.

  - All agents in this category are Schedule II opioids which have the highest potential for abuse and are associated with the risk of fatal overdoses due to respiratory depression.

  - Fentanyl carries a black box warning reminding prescribers that Schedule II opioids have the highest potential for abuse and are associated with the risk of fatal overdoses due to respiratory depression. This warning also recommends only using this product in patients who are already tolerant to opioid therapy.

  - Methadone also carries a black box warning discussing the cardiac and respiratory deaths that have been reported during initiation and conversion of pain patients to methadone treatment from other opioid agonists. It also warns of cases of QT interval prolongation and serious arrhythmias.

  - The extended release morphine products carry black box warnings stating that the tablets and capsules are to be swallowed whole to prevent rapid release and absorption of a potentially fatal dose of morphine. Avinza<sup>®</sup> has an additional warning about the concomitant use of alcohol resulting in a rapid release of the active ingredient and increased adverse events and overdose. MS Contin<sup>®</sup> and Kadian<sup>®</sup> 100 and 200 mg strengths also carry an additional warning to use these agents for opioid-tolerant patients only as use in patients not previously exposed to opioids may lead to fatal respiratory depression.

  - The black box warning for oxycodone ER describes the abuse potential and states the product is only for long-term use, and not as-needed treatment. This warning reminds practitioners that the tablets should be swallowed whole and that the 80 mg tablets are to be used with care in opioid-tolerant patients only.
Oxymorphone extended release carries a black box warning that the abuse liability is similar to that of other opioids, legal or illicit. The product should be swallowed whole and is not for as-needed use. Oxymorphone should not be used concomitantly with alcohol due to potential increase in blood levels of oxymorphone and potentially fatal overdose.

All agents in this class are contraindicated in patients who have acute or severe bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus. In addition, fentanyl transdermal system is contraindicated in patients who are not opioid-tolerant or for the treatment of acute or post operative pain.

All agents in this class are Pregnancy Category C with the exception of oxycodone controlled-release (B). Each of these agents has a long list of precautions, including head injury, use in geriatrics, renal and hepatic insufficiency, abdominal disorders, and cardiovascular disease. Please see individual product information for a complete listing.

Respiratory depression, hypotension, and profound sedation or coma may result if any of these agents are given concurrently with other narcotic analgesics, muscle relaxants, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, or other CNS depressants (including alcohol). Monoamine oxidase inhibitors may intensify the actions of opioids. Fentanyl and methadone are metabolized by the CYP450 enzyme system; therefore, coadministration with a CYP450 inducer or inhibitor should be performed with caution.

Several comparative trials have evaluated the long-acting narcotics:

- Methadone 7.5 mg Q12H and 5 mg Q4H PRN was compared to sustained release morphine 15 mg Q12H and immediate release 5 mg Q4H PRN in 103 patients with pain requiring initiation of a strong opioid. After 4 weeks, patients receiving methadone had more opioid-related dropouts (p=0.019). The two groups showed similar outcomes in opioid escalation at days 14 and 28 and in the reduction in pain intensity by day 8 and at 4 weeks.

- A 4 week randomized, placebo-controlled, double-blind trial of 295 patients with osteoarthritis who had previously failed to obtain adequate pain relief with NSAIDs and acetaminophen received morphine ER 30 mg once daily, morphine sulfate SR 15 mg twice daily or placebo. Both morphine products reduced pain and improved several sleep measures compared to placebo. Similar analgesic efficacy and similar occurrences of adverse reactions were seen in both morphine-treated groups.

- The analgesic efficacy and safety of oxymorphone ER (10-110 mg) was compared to oxycodone CR (20-220 mg) in 213 patients with moderate to severe chronic low back pain in a multicenter, randomized, double-blind, placebo- and active-controlled trial. The doses were titrated over 7-14 days. Those patients who achieved effective analgesia at a stable opioid dose entered an 18 day double-blind treatment phase and either continued opioid therapy or received placebo. Both opioids were found to be superior to placebo for change from baseline in pain intensity as measured on a visual analog scale (p=0.0001). Oxymorphone ER was equianalgesic to oxycodone CR at equianalgesic doses with comparable safety.

Because differences in chemical structure make cross-sensitivity less likely, patients who experience a systemic allergy, which may consist of a generalized rash or shortness of breath, to morphine, hydromorphone, oxymorphone, oxycodone or codeine may try methadone. For the treatment of pain, oxymorphone has identical uses to morphine; however, there is some evidence that oxymorphone may be associated with more nausea and vomiting. On the other hand oxymorphone may be less constipating than morphine.
ANALGESIC AGENTS

- Guidelines for pain management from the American Cancer Society and the American Society of Anesthesiologists recommend a stepwise approach with consideration for the type of pain and response to therapy. Initially, a non-opioid analgesic such as NSAIDs should be used. For mild to moderate pain, oral combinations of acetaminophen or NSAIDs with opioids are recommended. Adjunctive therapies such as tricyclic antidepressants or corticosteroids may be added. For moderate to severe pain, opioid analogics are the mainstay. Titration of the dose and frequency should be individualized to response and side effects. These guidelines further state that when tolerance to a particular opioid develops, another opioid may be substituted at approximately 50-75% of the equianalgesic dose.

RECOMMENDATION
According to current treatment guidelines, opioid analgesics are the mainstay of treatment for moderate to severe pain. When used properly, long-acting narcotics provide a decrease in administration frequency, longer periods of consistent pain control and a lower incidence of adverse effects than short-acting narcotics. However, these benefits come with greater abuse potential. There are no data to suggest than any one agent is superior to another; however, morphine is generally the agent most commonly used. Therefore, it is recommended that at least long-acting morphine be available. Methadone has utility in patients with allergy to other opioid analgesics, but it has a long half-life and is associated with significant risks including respiratory depression and cardiac arrhythmias. For this reason, methadone should be subject to clinical criteria restricting its use to patients who have tried and failed, or have a contraindication or intolerance to long-acting morphine. Furthermore, given concerns regarding fentanyl’s abuse potential and the risk of respiratory distress and overdose, fentanyl should be reserved for those who are opioid tolerant and unable to take (or absorb) oral opioids.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREferred</th>
<th>Non-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>KADIAN® QL (morphine sulfate, extended release pellets)</td>
<td>AVINZA® QL (morphine sulfate, extended release pellets)</td>
</tr>
<tr>
<td>MORPHINE SULFATE SA QL (Compares to MS Contin®, Oramorph SR®)</td>
<td>DOLOPHINE® CC, QL (methadone)</td>
</tr>
<tr>
<td>ORAMORPH SR® QL (morphine sulfate SA)</td>
<td>DURAGESIC® CC, QL (fentanyl)</td>
</tr>
<tr>
<td></td>
<td>FENTANYL PATCH CC, QL (Compares to Duragesic®)</td>
</tr>
<tr>
<td></td>
<td>METHADONE® CC, QL (Compares to Dolophine® and Methadose®)</td>
</tr>
<tr>
<td></td>
<td>METHADOSE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>MS CONTIN® QL (Compares to morphine sulfate SA)</td>
</tr>
<tr>
<td></td>
<td>OXYPHENVETALINE ER® QL (oxymorphone, extended release)</td>
</tr>
<tr>
<td></td>
<td>AVINZA® QL (morphine sulfate, extended release pellets)</td>
</tr>
<tr>
<td></td>
<td>DOLOPHINE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>DURAGESIC® CC, QL (fentanyl)</td>
</tr>
<tr>
<td></td>
<td>FENTANYL PATCH CC, QL (Compares to Duragesic®)</td>
</tr>
<tr>
<td></td>
<td>METHADONE® CC, QL (Compares to Dolophine® and Methadose®)</td>
</tr>
<tr>
<td></td>
<td>METHADOSE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>MS CONTIN® QL (Compares to morphine sulfate SA)</td>
</tr>
<tr>
<td></td>
<td>OXYPHENVETALINE ER® QL (oxymorphone, extended release)</td>
</tr>
<tr>
<td></td>
<td>AVINZA® QL (morphine sulfate, extended release pellets)</td>
</tr>
<tr>
<td></td>
<td>DOLOPHINE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>DURAGESIC® CC, QL (fentanyl)</td>
</tr>
<tr>
<td></td>
<td>FENTANYL PATCH CC, QL (Compares to Duragesic®)</td>
</tr>
<tr>
<td></td>
<td>METHADONE® CC, QL (Compares to Dolophine® and Methadose®)</td>
</tr>
<tr>
<td></td>
<td>METHADOSE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>MS CONTIN® QL (Compares to morphine sulfate SA)</td>
</tr>
<tr>
<td></td>
<td>OXYPHENVETALINE ER® QL (oxymorphone, extended release)</td>
</tr>
<tr>
<td></td>
<td>AVINZA® QL (morphine sulfate, extended release pellets)</td>
</tr>
<tr>
<td></td>
<td>DOLOPHINE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>DURAGESIC® CC, QL (fentanyl)</td>
</tr>
<tr>
<td></td>
<td>FENTANYL PATCH CC, QL (Compares to Duragesic®)</td>
</tr>
<tr>
<td></td>
<td>METHADONE® CC, QL (Compares to Dolophine® and Methadose®)</td>
</tr>
<tr>
<td></td>
<td>METHADOSE® CC, QL (methadone)</td>
</tr>
<tr>
<td></td>
<td>MS CONTIN® QL (Compares to morphine sulfate SA)</td>
</tr>
<tr>
<td></td>
<td>OXYPHENVETALINE ER® QL (oxymorphone, extended release)</td>
</tr>
</tbody>
</table>

The quantity limits and clinical criteria will not be included in this review, as they have recently been reviewed and approved by the Joint Committee for Narcotic Review, a sub-committee containing representatives from the PAC. All LA narcotics are subject to quantity limits requiring prior authorization for doses > 200 mg of morphine or morphine equivalent.
### References


LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

Acceptable reasons include:
- Allergy to medications not requiring prior approval
- Contraindication to or drug-to-drug interaction with medications not requiring prior approval
- History of unacceptable/toxic side effects to medications not requiring prior approval

The requested medication may be approved if both of the following are true:
- If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
- The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

The requested medication may be approved if the following is true:
- An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class within the Gastrointestinal Agents is organized into the following sections when applicable:

BACKGROUND:
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

RECOMMENDATION:
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
Background

- Gastroesophageal reflux refers to the retrograde movement of gastric contents from the stomach into the esophagus. When the esophagus is repeatedly exposed to refluxed material for prolonged periods of time, inflammation of the esophagus can occur. In severe cases, reflux may lead to serious complications such as esophageal strictures, esophageal ulcers, motility disorders, perforation, hemorrhage, aspiration and Barrett’s Esophagus.

- Peptic ulcer disease, on the other hand, refers to a group of ulcerative disorders of the upper gastrointestinal tract that require acid and pepsin for their formation. There are three common forms of peptic ulcer: Helicobacter pylori (H. pylori) associated, nonsteroidal anti-inflammatory drug (NSAID) associated, and stress ulcers. Chronic ulcers (H. pylori - and NSAID-associated) differ from acute ulcers (stress ulcers) in their depth, etiology, clinical presentation and tendency to recur.

- After oral administration, Proton Pump Inhibitors (PPIs) enter actively secreting parietal cells. At highly acidic pH, the agents are converted to a sulfonamide moiety which binds to the luminal surface of H⁺/K⁺-ATPase resulting in irreversible inhibition of the gastric proton pump and a long-lasting antisecretory effect.

- FDA-Approved Indications for Adults:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duodenal Ulcer</th>
<th>Dyspepsia</th>
<th>H. pylori</th>
<th>GERD</th>
<th>Erosive esophagitis</th>
<th>Hyper-secretory conditions</th>
<th>Gastroic Ulcers</th>
<th>NSAID-induced ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>esomeprazole</td>
<td></td>
<td>√</td>
<td>√</td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td>√</td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>omeprazole</td>
<td>√ Treatment</td>
<td>√</td>
<td>√</td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>omeprazole OTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omeprazole / sodium bicarbonate</td>
<td>√ Treatment</td>
<td>√</td>
<td></td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pantoprazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rabeprazole</td>
<td>√ Treatment</td>
<td>√</td>
<td></td>
<td></td>
<td>√ Treatment and Maintenance</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other FDA-Approved Indications:

- Esomeprazole is indicated for the short term treatment of GERD in children 12-17 years old.
- Lansoprazole is indicated for the short term treatment of GERD in children >1 year old and for short term treatment of erosive esophagitis in children 1-11 years old.
- Omeprazole is indicated for the treatment of GERD and other acid related disorders in children ≥ 2 years old.
- Omeprazole/sodium bicarbonate 40/1100 mg is indicated for upper GI bleeding prophylaxis in critically ill patients.
• The most common adverse reactions seen with PPIs include abdominal pain, diarrhea, headache and nausea.
  
  o All of the PPIs may rarely cause hip fracture and rhabdomyolysis. Other rare but serious side effects include:
    ▪ Severe skin rashes with esomeprazole, pantoprazole and rabeprazole.
    ▪ Pancreatitis, hepatotoxicity and interstitial nephritis with omeprazole.
    ▪ Hyperglycemia with pantoprazole.
  
  o PPIs should be used with caution in those with hepatic disease as dosage adjustments may be required. Lansoprazole, omeprazole and rabeprazole should be used with caution in patients with gastric malignancy as symptomatic response does not preclude the presence of gastric malignancy. The oral disintegrating lansoprazole tablets contain phenylalanine; therefore, this dosage form should be used with caution in phenylketonurics. The long term use of omeprazole may cause atrophic gastritis. Sodium bicarbonate (one of the components of Zegerid®) should be used with caution in patients with acid base balance problems, Bartter’s syndrome, hypocalcemia, hypokalemia, metabolic alkalosis and respiratory alkalosis. Omeprazole is Pregnancy Category C; however, all other agents in this class are Pregnancy Category B.
  
  o All PPIs have the potential to cause pH-dependent drug interactions resulting in a significant decrease in the absorption of weak bases, such as ketoconazole or itraconazole. Omeprazole inhibits CYP2C19 resulting in potential interactions with diazepam, phenytoin, and warfarin; however, esomeprazole dose not seem to have this interaction. Rabeprazole and pantoprazole do not interact with the CYP450 system significantly.

• There have been numerous comparative studies involving the various PPIs; however, the data has failed to clearly indicate clinical superiority for one agent over the others. Furthermore, studies have shown that most patients can be switched from one PPI to another without significant impact on efficacy or tolerability.
  
  o A double-blind, double-dummy, crossover trial randomized 240 patients to received daily treatment, first for 4 weeks with omeprazole 20 mg and, and then for 4 weeks with rabeprazole 20 mg. Each phase of 4 weeks was separately assessed by patients through questionnaires and by non-directed questioning about positive and negative side effects. At the end of the study period patients compared the two medications in seven treatment characteristics. Participants were also asked about their further attitude toward changing medications within the class. Results showed the majority of patients could be switched to another PPI without noticeable differences in ongoing primary symptom control. About 1/3 of patients were able to express a preference for one of the treatments. Favor was shown to rabeprazole for absence of unwanted side effects (p=0.0467) and presence of positive side effects (p=0.0188). However, no difference between the two PPIs was detected in the primary outcome variable of total treatment preference score. Most of the patients already controlled on a PPI (83.6%) indicated they would be willing to try another medication within the drug class.

• There are two main treatment strategies for GERD:
  
  o The “step up” approach uses an H2-receptor antagonist (H2RA) as initial therapy, and if it fails to relieve symptoms, the H2RA is changed to a PPI
  
  o The “step down” approach uses a PPI as initial therapy, and if the patient is symptom-free after 8 weeks, therapy is changed to an H2RA. The H2RA may then be stepped down over time to no medication depending on symptoms.
The 2005 guidelines from the American College of Gastroenterology (ACG) and the 2006 guidelines for the Institute for Clinical Systems Improvement (ICSI) recommend a “step down” approach to GERD. They recommend empiric therapy (therapy without diagnostic testing) with a trial of a standard-dose PPI for 4-8 weeks along with antacids and lifestyle modifications unless alarm symptoms are present such as dysphagia, odynophagia, bleeding, weight loss, or anemia are present. Patients with alarm symptoms, persistent symptoms of GERD or those who do not respond to a course of standard-dose PPI should undergo further diagnostic testing.

In contrast, the current guidelines from the Veteran Health Administration/Department of Defense (VHA/DoD) Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group state that empiric initial treatment may consist of either an H₂RA or PPI. They state that there is a lack of evidence and consensus to support using one treatment approach (step up, step down, or no step therapy) over the others. According to the VHA/DoD guidelines, expert opinion considers an H₂RA to be an appropriate first-line therapeutic option in patients without alarm symptoms or history of complicated GERD, and who have not undergone endoscopy, have negative endoscopy or have mild esophagitis.

The recommended acute doses of H₂RA are as follows:
- Cimetidine 400 mg BID or 800 mg QHS
- Famotidine 20 mg BID or 40 mg QHS
- Nizatidine 150 mg BID or 300 mg QHS
- Ranitidine 150 mg BID or 300 mg QHS

The VHA/DoD guidelines also state that symptom relief with standard doses of H₂RA usually occurs within 2 weeks and escalating the dose produces minimal to no benefit over switching to a PPI.

All 3 guidelines (ACG, ICSI and VAH/DoD) recommend endoscopy to screen for Barrett’s esophagus or esophageal adenocarcinoma in patients with a long duration of GERD symptoms (>5-10years). They also concur that there is little evidence favoring one PPI over another.

RECOMMENDATION
Proton Pump Inhibitors (PPIs) are a useful class of acid-suppressing drugs used for a variety of GI diagnoses. All agents within the PPI class have been shown to display similar safety and efficacy, and current guidelines do not differentiate between the available agents. Therefore, the PPIs can be considered therapeutic alternatives to one another. In order to ensure adequate patient and prescriber choice, it is recommended that at least 2 agents be available. Given that there are many different indications for the PPIs, including diagnoses for which H₂RAs have been shown to be effective, diagnoses requiring twice daily dosing, and diagnoses requiring specific tests to confirm them, it is recommended that this class of drugs be subject to clinical criteria to ensure appropriate use.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

REREVIEW: PROTON PUMP INHIBITORS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEXIUM® ST, QL (esomeprazole)</td>
<td>ACIPHEX® ST, QL (rabeprazole)</td>
</tr>
<tr>
<td>PREVACID® ST, QL (lansoprazole)</td>
<td>OMEPRAZOLE® ST, QL (compares to omeprazole)</td>
</tr>
<tr>
<td>PRILOSEC OTC® ST, QL (omeprazole)</td>
<td>PANTOPRAZOLE® ST, QL (compares to Protonix®)</td>
</tr>
<tr>
<td>(lansoprazole)</td>
<td>PREVACID SOLUTABS® ST, QL (lansoprazole)</td>
</tr>
<tr>
<td></td>
<td>PREVACID SUSPENSION® ST, QL (lansoprazole)</td>
</tr>
<tr>
<td></td>
<td>PREVACID NAPRAPAC® ST, QL (lansoprazole/naproxen)</td>
</tr>
<tr>
<td></td>
<td>PRILOSEC® ST, QL (omeprazole)</td>
</tr>
<tr>
<td></td>
<td>PROTONIX® ST, QL (pantoprazole)</td>
</tr>
<tr>
<td></td>
<td>ZEGERID® ST, QL (omeprazole/sodium bicarbonate)</td>
</tr>
</tbody>
</table>
Quantity Limits

<table>
<thead>
<tr>
<th>Medication</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciphex® 1/day</td>
<td>Prevacid NapraPAC® up to 84</td>
</tr>
<tr>
<td>Nexium® 1/day</td>
<td>Prevpac® 14/month</td>
</tr>
<tr>
<td>Omeprazole 1/day</td>
<td>Prilosec® 1/day</td>
</tr>
<tr>
<td>Pantoprazole 1/day</td>
<td>Prilosec OTC® 1/day</td>
</tr>
<tr>
<td>Prevacid® 1/day</td>
<td>Prilosec® 1/day</td>
</tr>
<tr>
<td>Prevacid® Solutabs 1/day</td>
<td>Zegerid® 1/day</td>
</tr>
<tr>
<td>Prevacid® Suspension 1/day</td>
<td></td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

The quantity limits and clinical criteria were recently reviewed by the committee; therefore, these will not be discussed at this time.

References


BACKGROUND

- Nausea is associated with altered physiologic activity, including the gastric hypomotility and increased parasympathetic tone that precede and accompany vomiting. Nausea may represent the awareness of the medullary vomiting center to the afferent stimuli such as systemic or ingested toxins, disturbance of the vestibular system, peritoneal inflammation or bowel obstruction. Psychogenic vomiting may be self-induced or may occur involuntarily in situations that are anxiety-inducing, threatening or in some way distasteful. The control of nausea and vomiting is much like the control of pain in that if nausea and vomiting is well controlled during the first exposure to an offending stimuli, psychogenic nausea and vomiting is less likely to occur during subsequent exposures to the same stimuli.
- Nausea and vomiting during chemotherapy appears to be associated with the release of serotonin from the enterochromaffin cells of the small intestine resulting in stimulation of vagal afferents through the 5-HT₃ receptors initiating the vomiting reflex. The oral 5-HT₃ antagonists, dolasetron, granisetron and ondansetron, selectively block the 5-HT₃ receptors which are found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines.
All agents in this class are indicated for the prevention of chemotherapy induced nausea and vomiting (CINV). Dolasetron is also indicated for the prevention and treatment of postoperative nausea and vomiting (PONV); however, ondansetron is only indicated for the prevention of PONV. In addition, granisetron and ondansetron are indicated for the prevention of nausea and vomiting as a result of radiation therapy. While prescribing information states that ondansetron can be used for patients over 4 years old, there are data to support its use in patients 6 months and older for PONV. Granisetron has been studied in limited randomized, controlled trials for PONV in patients older than 4 years old. Dolasetron is indicated for use in patients over 2 years old.

The most common adverse effects seen with the 5-HT₃ antagonists are headache, fatigue, diarrhea, hepatic function abnormalities and hypotension. Dolasetron may also cause tachycardia in ≥ 2% of patients.

- All of the 5-HT₃ antagonists should be used with caution in patients who have or may develop prolongation of cardiac conduction intervals such as QTc. All agents in this category are Pregnancy Category B. The dose of ondansetron should not exceed 8 mg per day in patients with severe hepatic impairment (Child-Pugh score >10).
- Due to variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT₃ antagonists than those used in adults may be required for antiemetic protection in children.

Several head-to-head comparative trials have been performed among the 5-HT₃ antagonists.

- A multicenter, randomized, double-blind study comparing dolasetron (single oral doses of 25, 50, 100 or 200 mg 1 hour prior to chemo) to ondansetron (8 mg given 1.5 hours prior, and 6.5, 14.5 and 22.5 hours after chemo) showed the two were therapeutically equivalent in the prevention of nausea and vomiting following moderately emetogenic chemotherapy.
- Granisetron (1 mg PO Q12H given on days 1 and 2) was compared to ondansetron (8 mg PO Q8H or 32 mg IV Q24H on days 1 and 2) in 102 patients prior to hematopoietic stem cell transplantation for the prevention of nausea and vomiting associated with high-dose chemotherapy or radiotherapy. There was no difference between the groups in overall complete response rates, overall major efficacy rates and mean visual analog scales (VAS) scores.
- Another double-blind, randomized, crossover study compared granisetron (3 mg/day) to ondansetron (24 mg/day) in 309 patients receiving two cycles of identical chemotherapy over 5 days. There was no statistical difference in the achievement of good control of emetic symptoms; however, patients preferred granisetron over ondansetron (p=0.048).
- An additional study compared ondansetron (4 mg, n=30), granisetron (1 mg, n=30) or granisetron (0.1 mg, n=28) in patients who experienced PONV, despite the preoperative use of ondansetron 4 mg, at the end of a surgical procedure requiring general anesthesia. There was no statistical difference between the three groups.

The 2006 guidelines from the American Society of Clinical Oncologists (ASCO) recommend a 5-HT₃ antagonist as first-line therapy in combination with aprepitant and dexamethasone for patients on chemotherapy of high or moderate emetic risk and those receiving an anthracycline (doxorubicin or epirubicin) and cyclophosphamide. For those patients receiving radiation therapy of all emetic risks, 5-TH₃ antagonists are recommended. These guidelines further state that “at equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably.”

In a 2007 update to their guidelines, the National Comprehensive Cancer Network (NCCN), in partnership with the American Cancer Society (ACS), stated that the choice of antiemetic should be based on the emetic risk of the chemotherapy as well as specific patient factors while noting that no one 5-HT₃ antagonist is more effective than another.
The 2003 guidelines from the International Anesthesia Research Society state that there is no evidence of any difference in the efficacy and safety profiles of the 5-HT₃ antagonists in the prophylaxis of PONV. For adults at moderate risk for PONV, prophylaxis should be considered using monotherapy or combination therapy. Double and triple antiemetic combinations are recommended for adults at high risk for PONV. All prophylaxis in children at moderate or high risk for PONV should be with combination therapy, using a 5-HT₃ antagonist and a second drug. If PONV occurs within 6 hours after surgery, patients should not receive a repeat dose of the prophylactic antiemetic.

RECOMMENDATION
Due to the high incidence of psychogenic vomiting, the goal of therapy for nausea and vomiting has become total control. The 2006 guidelines from the ASCO recommend a 5-HT₃ antagonist as first-line therapy for patients receiving chemotherapy of high and moderate emetic risk, an anthracycline (doxorubicin or epirubicin) and cyclophosphamide, or radiation therapy. According to the guidelines from the International Anesthesia Research Society, monotherapy or combination therapy using any of the antiemetic agents should be used for adults at moderate or high risk for PONV. All prophylaxis in children at moderate or high risk for PONV should be with combination therapy, using a 5-HT₃ antagonist and a second drug. These guidelines, along with those from the NCCN/ACS, make no differentiation between the available 5-HT₃ agents. The 5-HT₃ antagonists all exhibit similar efficacy and safety and can be considered therapeutic alternatives to one another. Therefore, it is recommended that at least one 5-HT₃ antagonist be available for patients receiving high or moderate emetic risk chemotherapy, for radiation therapy, and for those at high or moderate risk for PONV. In addition, it is recommended that at least one non-tablet formulation be available for use in the pediatric population or for those who have difficulty swallowing.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONDANSETRON CC, QL (Compares to Zofran tablets, solution, and orally disintegrating tablets)</td>
<td>ANZEMET® CC, QL (dolasetron tablets)</td>
</tr>
<tr>
<td>GRANISETRON CC, QL (Compares to Kytril tablets, solution)</td>
<td>KYTRIL® CC, QL (granisetron)</td>
</tr>
<tr>
<td>KYTRIL® SOLUTION CC (granisetron)</td>
<td>ZOFRAN® CC, QL (ondansetron tablets)</td>
</tr>
<tr>
<td>ZOFRAN OD³, CC, QL (ondansetron)</td>
<td>ZOFRAN® SOLUTION CC (ondansetron)</td>
</tr>
</tbody>
</table>

**Aloxi (palonosteron) will no longer be listed on the PDL because it is IV only.**

Quantity Limits
Anzemet = 1/month
Kytril = 2/month
Ondansetron 4 mg, 8 mg = 12/month; 24 mg = 1/month
Zofran 4 mg, 8 mg = 12/month; 24 mg = 1/month

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION
Clinical or Step Therapy

Ondansetron is unrestricted in patients less than 2 years old. Therapy may be approved for recipients meeting any one of the following criteria:

- Recipient is receiving highly emetogenic or moderately emetogenic chemotherapy, OR:
- Recipient is receiving radiation therapy, OR
- Recipient has a history of nausea and vomiting which has not responded to therapeutic doses of conventional antiemetics (i.e., metoclopramide, prochlorperazine, dexamethasone) or cannot take any of the conventional antiemetics due to adverse effects or contraindications, OR
- Recipient is being treated for post-operative nausea and vomiting (PONV).

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References

BACKGROUND

- The goal of antiemetic therapy is to prevent nausea and vomiting completely, and the American Society of Clinical Oncologists (ASCO) advises that complete control be used as a reference point when evaluating emetic situations. It is estimated that, with current treatment options, complete control of emesis is achieved in the majority of patients in the first 2 hours and 55% of patients during the first week of chemotherapy. While total control is ideal, lesser control (< 2 emetic episodes) or minor control (3-5 emetic episodes) may have value in difficult emetic situations.

- Aprepitant works by antagonizing brain substance NK₁ receptors which regulate the behavioral responses to a wide range of noxious and stressful stimuli.

- Aprepitant is approved for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy and for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in combination with other antiemetics. It is also approved for the prevention of postoperative nausea and vomiting (PONV).

- For the prevention of chemotherapy-induced nausea and vomiting (CINV), aprepitant is generally dosed at 125 mg before chemotherapy then 80 mg once daily for two days in combination with corticosteroids and 5-HT₃ antagonists. For the prevention of PONV, aprepitant is dosed at 40 mg up to three hours prior to induction of anesthesia.

- Common adverse effects associated with aprepitant include fatigue (17.8-21.9%), nausea (7.1-12.7%), hepatic abnormalities (6%), diarrhea (5.5-10.3%), headache (5-16.4%) and hypotension (0.5-3%). Aprepitant may also cause proteinuria in as many as 6.8% of patients.

  - Aprepitant is metabolized via the CYP3A4 enzyme system; therefore, there is potential for interactions with inhibitors or inducers of this enzyme system. Because of this route of metabolism, the concomitant use of aprepitant and pimozide, terfenadine, astemizole or cisapride is contraindicated. Aprepitant may also induce the CYP2C9 enzyme. There is potential for decreased INR levels if administered to patients concomitantly receiving warfarin, and the dose of corticosteroid should be reduced by 50% if coadministered with aprepitant. The effects of oral contraceptive pills may be decreased if given along with aprepitant as well.

- Patients were assigned to receive either aprepitant 375 mg an hour before cisplatin on day 1 and 250 mg on days 2-3 (n=35), aprepitant 125 mg before cisplatin and 80 mg on days 2-5 (n=81), or placebo before cisplatin on days 2-3 (n=86). In addition, all groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin and dexamethasone 8 mg on days 2-5. The aprepitant 375/250 mg arm was discontinued early due to new pharmacokinetic data resulting in an alteration in recommended dosing. In the first cycle, aprepitant was superior to standard therapy (64% vs. 49%) in complete response rates (p=<0.05). By cycle 6 aprepitant complete response rates were still 59%; however, standard therapy had decreased to 34% complete response (p=<0.05).
The safety and efficacy of aprepitant was evaluated when administered alone or in combination with ondansetron in a randomized, double-blind, placebo-controlled study using 243 women who underwent abdominal hysterectomy. Recipients (n=86) received either aprepitant 100 mg versus placebo or 200 mg versus placebo orally 60-90 minutes before induction of anesthesia. A second group of patients (n=157) received either aprepitant 200 mg or placebo 60-90 minutes before induction of anesthesia and ondansetron 4 mg or placebo intravenously 15-30 minutes before the end of surgery. Pain and nausea levels were assessed on arrival in the postanesthesia care unit and at 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hour intervals postoperatively. Results showed that only 10% of patients who had received aprepitant 200 mg experienced emesis within the first 8 hours after surgery compared to 50% of those who had received placebo. Aprepitant also decreased the need for rescue medication (25% versus 48%); however, aprepitant 100 mg was less effective than 200 mg in decreasing the incidence of repeated episodes of emesis. Six percent of the patients receiving aprepitant 200 mg orally experienced emesis less than 2 hours after surgery compared with 17% with ondansetron alone (p=<0.05). Only 2% of those who received combination therapy experienced emesis compared to ondansetron alone (p=<0.05). The median times for 75% of patients to remain free from postoperative nausea and vomiting were 82, 75 and 362 minutes in the ondansetron, aprepitant, and combination groups, respectively (p=<0.05).

The 2006 ASCO guidelines place aprepitant as first-line therapy in combination with a 5-HT3 antagonist and dexamethasone for patients on chemotherapy of high emetic risk and those receiving an anthracycline (doxorubicin or epirubicin) and cyclophosphamide. These guidelines also consider aprepitant in combination with dexamethasone as first-line therapy for the prevention of delayed emesis with agents of high emetic risk.

The 2003 guidelines from the International Anesthesia Research Society state that for adults at moderate risk for PONV, prophylaxis should be considered using monotherapy or combination therapy. Double and triple antiemetic combinations are recommended for adults at high risk for PONV. All prophylaxis in children at moderate or high risk for PONV should be with combination therapy using a 5-HT3 antagonist and a second drug. If PONV occurs within 6 hours after surgery, patients should not receive a repeat dose of the prophylactic antiemetic.

**RECOMMENDATION**

Aprepitant is a NK1 receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting (CINV) associated with highly or moderately emetogenic cancer chemotherapy as well as for the prevention of postoperative nausea and vomiting (PONV). Current treatment guidelines from the ASCO place aprepitant (along with a 5-HT3 antagonist and dexamethasone) as first-line therapy for the treatment of CINV when chemotherapeutic agents with high potential for emesis are used or in those patients receiving an anthracycline and cyclophosphamide. These guidelines also consider aprepetant in combination with dexamethasone as first-line therapy for the prevention of delayed emesis with agents of high emetic risk. Guidelines from the International Anesthesia Research Society recommend double and triple antiemetic combinations for adults at high risk for PONV. Therefore, it is recommended that aprepetant be available for use in patients receiving chemotherapy with a high potential for emesis, in patients receiving an anthracycline and cyclophosphamide, or for those at high risk for PONV.

**COMMITTEE VOTE:**

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

**REREVIEW: ORAL ANTI-EMETICS: NK-1 ANTAGONISTS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>EMEND® CC, QL</td>
</tr>
<tr>
<td>(aprepitant)</td>
<td></td>
</tr>
</tbody>
</table>
Quantity Limits
Emend 80 mg = 2/RX; 40 mg, 125 mg, and Tripack = 1/RX

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

Clinical Criteria for Emend®
May only be approved for ONE of the following indications:

- Is receiving a highly emetogenic chemotherapy regimen or the combination of an anthracycline (doxorubicin or epirubicin) and cyclophosphamide, OR:
- Is receiving a moderately emetogenic chemotherapy regimen and has failed other previous antiemetic regimens, OR
- Is being treated for post-operative nausea and vomiting and has tried and failed or has a contraindication to a 5HT₃-receptor antagonist, OR
- Has refractory nausea that would require hospitalization, OR
- Has an ER admission that has failed on 3 conventional treatments (i.e., metoclopramide, prochlorperazine, 5HT₃- antagonists), or if these agents are contraindicated.

Therapy may be approved for 3 days. Note- if chemotherapy is more frequent than once a week, may approve a quantity sufficient for 3 days beyond the chemotherapy duration. Chronic continuous administration is not recommended.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

References
LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

Acceptable reasons include:
- Allergy to medications not requiring prior approval
- Contraindication to or drug-to-drug interaction with medications not requiring prior approval
- History of unacceptable/toxic side effects to medications not requiring prior approval

The requested medication may be approved if both of the following are true:
- If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
- The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

The requested medication may be approved if the following is true:
- An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

--------------------------------------------------------------------------------------------------------------------------------

The information provided for each drug class within the Ophthalmics Agents is organized into the following sections when applicable:

BACKGROUND:
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

RECOMMENDATION:
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
BACKGROUND

• The ophthalmic antihistamines are most commonly used in the treatment of conjunctivitis, which may occur secondary to infectious or non-infectious stimuli. Allergic conjunctivitis occurs as a result of exposure to allergens with symptoms including itching, redness, swelling and mucous discharge.

• For purposes of this review, we will focus on the available prescription ophthalmic antihistamines, including azelastine, emedastine, epinastine, olopatadine and ketotifen.

• The ophthalmic antihistamines’ mechanism of action is exerted through antagonism of the H_1 histamine receptor; in addition, with the exception of emedastine, these products inhibit other mediators involved in allergic reactions.

• All of the ophthalmic antihistamines are FDA-approved for the treatment or prevention of signs and symptoms associated with allergic conjunctivitis.

• The most frequently reported adverse reactions with the ophthalmic antihistamines are: eye burning/stinging, blurred vision, headaches, bitter taste and rhinitis. Due to the topical administration of the products, most of the adverse effects are mild and transient.

  o The ophthalmic antihistamines are all categorized as Pregnancy Category C, with the exception of emedastine, which is Pregnancy Category B.

  o Due to the topical administration of the ophthalmic antihistamines, systemic absorption is minimal; therefore, clinically significant drug interactions are not well defined.

• Many of the studies comparing the ophthalmic antihistamines are single-dose studies using the conjunctival allergen challenge (CAC) model which attempts to induce an allergic response and evaluate drug efficacy in a short-term study. Because of design limitations, these studies give little information regarding long-term efficacy and safety with chronic use of these agents.

  o Sixty-six patients were evaluated in a prospective, randomized, double-blind study to determine the safety and efficacy of olopatadine compared to epinastine using the CAC model. Patients received either olopatadine in one eye with epinastine in the other eye, olopatadine in one eye with placebo in the other eye, or epinastine in one eye with placebo in the other eye. Olopatadine was associated with less itching (p=0.003), conjunctival redness (p<0.001), chemosis (p<0.001), ciliary redness (p<0.001) and episcleral redness (p<0.001) than epinastine.

  o A randomized CAC study comparing ketotifen and olopatadine was conducted in 53 patients. Patients received one drop of each agent in contra lateral eyes. Efficacy scores for olopatadine were significantly higher than ketotifen at both three and five minutes post-challenge (p<0.05). In addition, olopatadine was rated more comfortable than ketotifen immediately and 12 hours post-challenge (p<0.05).

• Sixty-six patients with seasonal allergic conjunctivitis were studied for efficacy of ketotifen and olopatadine. Patients were treated with either ketotifen or olopatadine twice daily and were assessed on days 5 and 21. Responder rates were higher for ketotifen versus olopatadine on both days 5 and 21 (72% vs. 54% on day 5; 91% vs. 55% on day 21). Severity scores for hyperemia and itching were lower for the ketotifen group as well. However, patients rated both drugs similarly for comfort.

• The American Academy of Ophthalmology (AAO) and the American Optometric Association (AOA) both recommend that treatment of allergic conjunctivitis be based upon elimination of the offending allergens. The use of pharmacological agents, including ophthalmic antihistamines, may be useful in treating the associated symptoms. Neither the AAO nor the AOA makes a differentiation between the available agents in this class.
OPHTHALMIC AGENTS

RECOMMENDATION
The ophthalmic antihistamines are FDA-approved for the treatment or prevention of the signs and symptoms associated with allergic conjunctivitis. The AAO and the AOA both recommend that treatment of allergic conjunctivitis start with removal of the offending allergens and that pharmacological agents, including ophthalmic antihistamines, may be useful in treating the associated symptoms. The recommendations make no differentiation between the available agents in this class; therefore, all agents may be considered therapeutically equivalent. It is recommended that at least two ophthalmic antihistamines be available for use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: OPHTHALMIC ANTIHISTAMINES

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATADAY® (olopatadine)</td>
<td>ELESTAT® (epinastine)</td>
</tr>
<tr>
<td>PATANOL® (olopatadine)</td>
<td>EMADINE® (emedastine)</td>
</tr>
<tr>
<td>OPTIVAR® (azelastine)</td>
<td>KETOTIFEN (compares to Zaditor®)</td>
</tr>
<tr>
<td></td>
<td>ZADITOR® (ketotifen)</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

References

REREVIEW: OPHTHALMIC MAST CELL STABILIZERS

BACKGROUND
- Vernal keratoconjunctivitis (VKC), vernal conjunctivitis and vernal keratitis all refer to chronic, bilateral conjunctival inflammation with photophobia and itching that recurs seasonally during warm weather. Allergic conjunctivitis occurs as a result of exposure to allergens with symptoms including itching, redness, swelling and mucous discharge.
- The ophthalmic mast cell stabilizers, including cromolyn, lodoxamide, nedocromil and pemirolast, inhibit the degranulation of sensitized mast cells which occurs during the immediate hypersensitivity reaction. In addition, mast cell stabilizers act by inhibiting the release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from the mast cell.
- FDA approved indications are as follows:
  - cromolyn sodium and lodoxamide: treatment of vernal keratoconjunctivitis, vernal conjunctivitis and vernal keratitis
  - nedocromil and pemirolast: treatment of itching associated with allergic conjunctivitis
- The most common adverse effect associated with ophthalmic use of the mast cell stabilizers is a burning or stinging sensation in the eye. Other common adverse effects include: blurred vision, headache and unpleasant taste.
  - All of the ophthalmic mast cell stabilizers are Pregnancy Category C.
Due to the topical administration of the ophthalmic mast cell stabilizers, systemic absorption is minimal; therefore, clinically significant drug interactions are not well defined.

- Thirty-six patients with VKC were randomized to receive either nedocromil or cromolyn eye drops four times daily for 5 months. Nedocromil took effect sooner and was superior to cromolyn in relief of itching, grittiness, hyperemia and keratitis at 6 weeks (p<0.05) and of hyperemia (p<0.01), keratitis, papillae and pannus (p<0.001) at 22 weeks. Both treatments were well tolerated.
- Thirty patients with VKC were enrolled in a randomized trial of topical lodoxamide and topical cromolyn. Both treatment groups showed significant improvements over pre-treatment scores; however, symptom scores of the lodoxamide group were significantly lower than those in the cromolyn group.
- 120 patients with VKC were enrolled in a double-blind study to determine the effectiveness of ophthalmic lodoxamide versus cromolyn. Efficacy was measured by alleviation of the primary symptoms of VKC, including itching, tearing, foreign-body sensation, and discomfort. Lodoxamide was found to be at least as effective as cromolyn in the treatment of VKC.
- The AAO and the AOA both recommend that treatment of allergic conjunctivitis be based upon elimination of the offending allergens. The use of pharmacological agents, including ophthalmic antihistamines and mast cell stabilizers, may be useful in treating the associated symptoms. Neither the AAO nor the AOA makes a differentiation between the available agents in this class. Ophthalmic mast cell stabilizers are usually considered in patients with symptoms that are present throughout the allergy season or patients with VKC who require long-term control. They may also be beneficial in patients not responding to or not tolerating ophthalmic antihistamines.

**RECOMMENDATION**

The ophthalmic mast cell stabilizers are FDA-approved for the treatment of itching associated with allergic conjunctivitis or for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis and vernal keratitis. The AAO and the AOA both recommend that treatment of allergic conjunctivitis start with removal of the offending allergens and that pharmacological agents, including ophthalmic mast cell stabilizers, may be useful in treating the associated symptoms. Ophthalmic mast cell stabilizers are usually considered in patients with symptoms that are present throughout the allergy season or patients with VKC who require long-term control. The current recommendations make no differentiation between the available agents in this class; therefore, all agents may be considered therapeutic alternatives to one another. In order to ensure patient and prescriber choice, it is recommended that at least two ophthalmic mast cell stabilizers be available for use.

**COMMITTEE VOTE:**

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

**REFERENCES**

BACKGROUND

- Primary open-angle glaucoma is a chronic, progressive disease resulting in damage to the optic nerve and visual field abnormality which may be due to increased intraocular pressure (IOP) as well as other factors. The goal of therapy for glaucoma is to limit damage to the optic nerve, delay the need for surgery and prevent functional vision loss, which may be accomplished by decreasing IOP.

- The ophthalmic prostaglandin agonists reduce IOP by increasing uveoscleral outflow of aqueous humor from the anterior chamber of the eye. Additionally, bimatoprost reduces IOP by increasing trabecular outflow.

- The ophthalmic prostaglandin agonists are FDA-approved for the reduction of elevated IOP in ocular hypertension and open-angle glaucoma. However, latanoprost and travoprost are only approved for patients who are intolerant of or inadequately respond to other IOP lowering medications.

- Common adverse effects associated with the use of prostaglandin agonists include: eyelash changes, increased brown pigmentation of iris and eyelid skin, and conjunctival hyperemia.
  - All of the ophthalmic prostaglandin agonists are Pregnancy Category C.
  - Ophthalmic products containing thimerosal should be administered at least five minutes apart from latanoprost due to the potential for precipitation.

- There are numerous comparative trials available for the ophthalmic prostaglandin agonists.
  - A 12-week, randomized, parallel-group study involving 410 patients with open-angle glaucoma or ocular hypertension compared the IOP-lowering effects and tolerability of latanoprost, bimatoprost and travoprost. All agents exhibited similar IOP reductions over the study period with no statistically significant differences between agents. With regards to tolerability, patients in the latanoprost group experienced less hyperemia or other ocular adverse events compared to the other two groups (results were significant compared to bimatoprost), (p<0.001).
  - Bimatoprost and latanoprost have been compared for safety and efficacy in five separate studies. All of the studies found bimatoprost to lower the IOP more than latanoprost; however, this difference only reached statistical significance in three of the five studies. Conjunctival hyperemia was found more commonly in the bimatoprost group in three of the five studies, the remaining two studies found no difference in adverse event rates between the two groups.
  - Bimatoprost and travoprost have been compared for safety and efficacy in four studies. Both therapies significantly lowered IOP in all four studies with more patients receiving bimatoprost achieving target IOP; however, the difference between the two treatment groups failed to meet statistical significance in two of the studies. There were no differences in adverse event rates in any of the four studies.

- The treatment of glaucoma should focus on achieving target IOP, which often requires combination therapy. Current guidelines from the AAO and the Royal College of Ophthalmologists (RCO) suggest that topical prostaglandin agonists and topical beta-agonists are considered eye drops of “first choice” for the treatment of glaucoma, though the guidelines do not distinguish between individual agents in the class.
RECOMMENDATION
Ophthalmic prostaglandin agonists are approved for the reduction of elevated IOP in ocular hypertension and open-angle glaucoma. Current guidelines from the AAO and the RCO suggest that topical prostaglandin agonists and topical beta-agonists are considered eye drops of “first choice” for the treatment of glaucoma. Studies show that bimatoprost may be more effective than other prostaglandin agonists at decreasing IOP, but this added benefit may be offset by an increase in the incidence of conjunctival hyperemia. Current treatment guidelines make no differentiation between the available agents in this class. With these considerations, it is recommended that at least one prostaglandin agonist be available for use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>REVIEW: OPHTHALMIC PROSTAGLANDIN AGONISTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>LUMIGAN® (bimatoprost)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Quantity Limits

| LUMIGAN® 2/month (in billing units of 2.5 mL) |
| 1/month (in billing units of 7.5 mL) |
| TRAVATAN® 4/month (in billing units of 2.5mL) |
| TRAVATAN Z® 4/month (in billing units of 2.5mL) |
| XALATAN® 2/month (in billing units of 2.5mL) |

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References


REREVIEW: OPHTHALMIC CARBONIC ANHYDRASE INHIBITORS

BACKGROUND

- This review will focus on the ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, as well as the combination dorzolamide/timolol product (Cosopt®).
- The ophthalmic carbonic anhydrase inhibitors reduce IOP by decreasing aqueous humor production via inhibition of carbonic anhydrase in the ciliary processes of the eye. Cosopt® decreases aqueous humor production through both carbonic anhydrase inhibition and beta-blockade; the timolol component may also increase outflow.
• The ophthalmic carbonic anhydrase inhibitors are FDA-approved for the reduction of elevated IOP in patients with ocular hypertension and open-angle glaucoma. Cosopt® is indicated for the reduction of elevated IOP in patients with ocular hypertension and open-angle glaucoma who inadequately respond to topical beta blocker therapy alone.

• Common adverse events related to the use of ophthalmic carbonic anhydrase inhibitors include bitter taste and instillation reactions, both of which are more common with the use of dorzolamide than brinzolamide.
  
  o Due to the potential for systemic absorption of timolol, Cosopt® is contraindicated in patients with bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree heart block, cardiac failure or cardiogenic shock.
  
  o Dorzolamide and brinzolamide are sulfonamides and can be systemically absorbed with ophthalmic use. Adverse reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis and aplastic anemia are possible. Topical beta-blockers have also been shown to have systemic absorption that may produce systemic adverse effects, including bronchospasm and masking of the signs and symptoms of hypoglycemia.
  
  o Dorzolamide has not been studied in severe renal or hepatic impairment and therefore, its use is not recommended in this patient population.
  
  o All of the ophthalmic carbonic anhydrase inhibitors are Pregnancy Category C.

• Brinzolamide and dorzolamide were compared for efficacy, safety and tolerability in a randomized, double-blind, placebo-controlled study of 463 patients. All therapies were similar in efficacy, measured as a reduction in IOP. Burning and stinging were significantly higher with dorzolamide than brinzolamide (12.2% vs. 3%, p<0.05).

• Cosopt® was compared to its individual components in a two part study. One hundred thirty-one patients were enrolled in part 1 of the study, which randomized patients to receive either Cosopt® or a topical carbonic anhydrase inhibitor + a non-selective beta blocker given BID. The differences in reduction in IOP were not statistically significant between the two groups. Part 2 of the study enrolled 404 glaucoma patients maintained on dorzolamide + a beta blocker and converted these patients to the combination product. After one month of combination therapy, the IOP was reduced by an additional 1.7 mm Hg (p<0.001). However, when comparing dorzolamide given TID + timolol given BID to the combination product given BID, the individual components provide slightly greater IOP lowering per Cosopt® product labeling.

• Current guidelines from the AAO and RCO suggest that topical prostaglandin agonists and topical beta-agonists are considered eye drops of “first choice” for the treatment of glaucoma and ocular hypertension. However, treatment should focus on achieving target IOP, which often requires combination therapy. If a second agent is required, carbonic anhydrase inhibitors or alpha-2 agonists are usually considered as viable options. The role of Cosopt® is in patients who have had a suboptimal response to beta-blocker therapy alone; however, studies suggest that the individual components may be more effective than the combination product when given at approved doses. The combination product may also be useful when patient compliance is an issue.
OPHTHALMIC AGENTS

RECOMMENDATION
The carbonic anhydrase inhibitors are FDA-approved for the reduction of elevated intraocular pressure in ocular hypertension and open-angle glaucoma. Current guidelines from the AAO and the RCO suggest that topical prostaglandin agonists and topical beta-agonists are considered “first choice” topical agents for the treatment of glaucoma and ocular hypertension. However, treatment should focus on achieving target IOP, which often requires combination therapy. If a second agent is required, carbonic anhydrase inhibitors or alpha-2 agonists are usually considered as viable options. Available guidelines make no differentiation between the available agents in this class. Based on the current guidelines and clinical literature, the carbonic anhydrase inhibitors appear to produce similar reductions in IOP and can thus be considered therapeutic alternatives to one another. It is recommended that at least one ophthalmic carbonic anhydrase inhibitor be available for use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: OPHTHALMIC CARBONIC ANHYDRASE INHIBITORS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZOPT® QL (brinzolamide)</td>
<td>N/A</td>
</tr>
<tr>
<td>COSOPT® QL (timolol/dorzolamide)</td>
<td>N/A</td>
</tr>
<tr>
<td>TRUSOPT® QL (dorzolamide)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Quantity Limits
Azopt® 3/month (in billing units of 5 mL)
Cosopt® 3/month (in billing units of 5 mL)
Trusopt® 3/month (in billing units of 5 & 10 mL)

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References
BACKGROUND

- Bacterial conjunctivitis presents with itching, burning eyes with purulent discharge, usually unilaterally. Although self-limiting in most cases, topical antibiotics are applied in many infections in an attempt to prevent the spread of conjunctivitis to others. Serious infection of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. Infections that could threaten vision may require broad-spectrum antibiotics. The agents in this category contain various combinations of bacitracin, dexamethasone, gramicidin, hydrocortisone, neomycin, polymyxin B, prednisolone, sulfacetamide and trimethoprim.

- These agents have varying mechanisms of action.
  - Bacitracin inhibits bacterial growth by preventing cell wall subunits from being added to the peptidoglycan chain.
  - Gramicidin increases bacterial cell permeability to inorganic cations by forming a network of channels through the lipid bilayer of the membrane.
  - Neomycin, along with the other aminoglycosides, inhibits protein synthesis by binding to the 3OS ribosomal subunit.
  - Polymyxin B increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.
  - Folic acid is essential for bacterial transport of one-carbon fragments and for the synthesis of thymidine, purines and certain amino acids. Sulfacetamide inhibits bacterial dihydrofolate synthetase, the enzyme responsible for the conversion of p-aminobenzoic acid (PABA) into folic acid.
  - Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by interfering with folate synthesis.
  - Corticosteroids (dexamethasone, hydrocortisone and prednisolone) work by suppressing the inflammatory response to a variety of agents.

- All of the products containing a corticosteroid are indicated for inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists. There are no specific indications for the ophthalmic steroids in pediatric patients; however, data are available for patients greater than 2 months of age for prednisolone/sulfacetamide. The FDA-approved indications for the antibiotic agents are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacitracin</td>
<td>Superficial ocular infections involving the conjunctiva or cornea</td>
<td>Not specified</td>
</tr>
<tr>
<td>bacitracin/poly B</td>
<td>Superficial ocular infections involving the conjunctiva or cornea</td>
<td>Not specified</td>
</tr>
<tr>
<td>neomycin/poly B/bacitracin</td>
<td>Conjunctivitis</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Superficial ocular infection</td>
<td></td>
</tr>
<tr>
<td>neomycin/poly B/gramicidin</td>
<td>Conjunctivitis</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Superficial ocular infection</td>
<td></td>
</tr>
<tr>
<td>polymyxin B/TMP</td>
<td>Conjunctivitis</td>
<td>&gt; 2 months</td>
</tr>
<tr>
<td></td>
<td>Blepharocconjunctivitis</td>
<td></td>
</tr>
<tr>
<td>sulfacetamide</td>
<td>Conjunctivitis</td>
<td>&gt; 2 months</td>
</tr>
<tr>
<td></td>
<td>Corneal ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlamydial conjunctivitis including trachoma and inclusion conjunctivitis</td>
<td></td>
</tr>
</tbody>
</table>
• The spectrums of action of the agents in this class vary.
  o Bacitracin has broad coverage of gram positive organisms.
  o Polymyxin has broad coverage of gram negative organisms including *Proteus mirabilis, Pseudomonas aeroginosa,* and *Serratia marcescens.*
  o Neomycin has mixed gram positive and gram negative activity; however, its gram positive coverage is not as broad as bacitracin, and it lacks some of the gram negative activity of polymyxin, such as *Pseudomonas.*
  o Gramicidin has a spectrum similar to bacitracin, targeting solely gram positive organisms.
  o Sulfacetamide has broad spectrum activity against *E. coli, S. aureus, S. pneumoniae, Streptococcus* (viridans group), *H. influenzae, Klebsiella* species and *Enterobacter* species.
  o Trimethoprim has mixed gram positive and gram negative activity, including *Staphylococcus* species, *S. pneumoniae, E. coli, H. influenzae, K. pneumoniae* and *P. mirabilis.*

• The most common adverse effects seen with the non-quinolone ophthalmic antibiotics are localized ocular toxicity and hypersensitivity, lid itching, lid swelling, and conjunctival erythema. Serious hypersensitivity reactions including anaphylaxis and secondary fungal and viral infections have occurred rarely. The steroid component may frequently cause increased intraocular pressure (IOP) which may result in glaucoma. Infrequently optic nerve damage, cataract formation, and delayed wound healing may occur. Secondary fungal infections have been reported as well.

  o The combination products containing a steroid are contraindicated in most viral diseases of the cornea and conjunctiva, in mycobacterial infections of the eye and in fungal diseases of ocular structures.
  o Prolonged use of corticosteroids may result in glaucoma and increased susceptibility to other ocular infections. If an ophthalmic steroid is used for longer than 10 days, it is recommended that IOP be monitored.

• There is very little comparative data of good quality from the US for the medical management of bacterial conjunctivitis due to a large portion of study patients not completing the study period. However *in vitro* susceptibility has been studied.
  o Isolates from clinically symptomatic eyes (n=454) were tested for susceptibility to ciprofloxacin, norfloxacin, ofloxacin, gentamicin, neomycin, tobramycin, bacitracin, erythromycin and chloramphenicol. Results showed the fluoroquinolones were very effective against the gram-negative organisms but were not as effective against the gram-positive organisms such as coagulase-negative *Staphylococcus* and *S. viridans.* Bacitracin and chloramphenicol showed good *in vitro* activity against gram-positive organisms. While no antibiotic demonstrated 100% coverage, results showed the overall *in vitro* efficacy in descending order is as follows: chloramphenicol, ciprofloxacin, ofloxacin, norfloxacin, bacitracin, tetracycline, neomycin, erythromycin, tobramycin and gentamicin.

• Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can act as a physical barrier and impede delivery of other ophthalmic drugs. Ointments are usually most useful in young children as they decrease the loss of drug due to tear production and are often easier to administer. Ophthalmic suspensions less rapidly mix with tears and remain in the cul-de-sac longer than solutions.
There appears to be a lack of good quality literature comparing antibiotics of any type with placebo for the treatment of acute bacterial conjunctivitis. Treatment guidelines from the American Optometric Association (AOA) state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patient's age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice.

The American Academy of Ophthalmology (AAO) also recommends a course of broad spectrum antibiotics for empiric therapy for bacterial conjunctivitis. In addition, the AAO recommends bacitracin, as well as cefazolin, vancomycin, moxifloxacin or gatifloxacin, for the treatment of bacterial keratitis in which the causative organisms are gram positive cocci.

In general the use of an antibiotic/corticosteroid combination drug is indicated where the risk of superficial ocular infection is high or where there is the expectation that dangerous numbers of bacteria will be present in the eye. The AOA guidelines specifically recommend the use of topical antibiotic/steroid combinations in the treatment of herpes zoster conjunctivitis to reduce the risk of secondary bacterial infection and decrease the inflammatory response. While topical steroids are contraindicated in viral conjunctivitis, they do not exacerbate herpes zoster infections. Symptomatic patients with toxic conjunctivitis may benefit from cold compresses and/or topical ophthalmic antibiotic/corticosteroid combinations, and phlyctenular conjunctivitis responds to topical use of an antibiotic/corticosteroid combination. Again, the AOA does not name an antibiotic/corticosteroid combination of choice.

RECOMMENDATION
The non-quinolone ophthalmic antibiotics are often used for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum topical antibiotics are the treatment of choice for bacterial conjunctivitis. All of the products in this category, with the exception of bacitracin, offer broad spectrum coverage of both gram positive and gram negative organisms, and therefore, can be considered therapeutic alternatives for empiric treatment of bacterial conjunctivitis. Based on this information, it is recommended that at least 3 non-quinolone antibiotics be available, two that offer broad spectrum coverage of gram positive and gram negative organisms and bacitracin for gram positive coverage. It is also recommended that there be at least one solution and one ointment dosage form available.

Antibiotic/corticosteroid combination products are indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is an expectation that dangerous numbers of bacteria will be present in the eye. The AOA specifically recommends these combination products for the treatment of herpes zoster, toxic conjunctivitis and phlyctenular conjunctivitis. The AOA makes no differentiation between the available ophthalmic steroid/antibiotic products in their guidelines. Therefore, it is recommended that at least two combination steroid/antibiotic products be available. In order to allow for patient and provider choice, it is recommended that there be at least one solution and one ointment dosage form available as well.

COMMITTEE VOTE:
APPROVED     DISAPPROVED     APPROVED with MODIFICATION
REREVIEW: OPHTHALMIC ANTIBIOTICS NON-QUINOLONE AND COMBINATIONS

<table>
<thead>
<tr>
<th>REFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>BACITRACIN</td>
</tr>
<tr>
<td>BACITRACIN/POLY B (Compares to Polysporin®, AK Poly® ointment)</td>
</tr>
<tr>
<td>NEOMYCIN/POLY B/GRAMICIDIN (Compares to Neosporin® ointment)</td>
</tr>
<tr>
<td>NEOMYCIN/POLY B/HC (Compares to Cortisporin® ointment, solution)</td>
</tr>
<tr>
<td>NEOMYCIN/BAC/POLY B/HC</td>
</tr>
<tr>
<td>NEOMYCIN/POLY B/DEXAMETHASONE (Compares to Maxitrol® ointment, suspension)</td>
</tr>
<tr>
<td>NEOMYCIN/POLY B/PREDNISOLONE (Compares to Poly-Pred® suspension)</td>
</tr>
<tr>
<td>POYMIXIN B/TMP (Compares to Poltrim®)</td>
</tr>
<tr>
<td>SULFACETAMIDE SODIUM (Compares to Bleph-10® solution)</td>
</tr>
<tr>
<td>SULFACETAMIDE/PREDNISOLONE (Compares to Blephamide®, Vasocidin®)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK-POLY BAC® (bacitracin/poly B ointment)</td>
</tr>
<tr>
<td>BLEPH-10® (sulfacetamide solution)</td>
</tr>
<tr>
<td>BLEPHAMIDE® (sulfacetamide/prednisolone ointment, suspension)</td>
</tr>
<tr>
<td>CORTISPORIN® (neomycin/poly B. HC)</td>
</tr>
<tr>
<td>MAXITROL® (neomycin/poly B/dexamethasone solution)</td>
</tr>
<tr>
<td>NEOSPORIN® (neomycin/poly B/bacitracin ointment)</td>
</tr>
<tr>
<td>NEOSPORIN® (neomycin/poly B/gramicidin solution)</td>
</tr>
<tr>
<td>POLY-PRED® (neomycin/poly B/prednisolone suspension)</td>
</tr>
<tr>
<td>POLYSPORIN® (bacitracin/poly B ointment)</td>
</tr>
<tr>
<td>POLYTRIM® (Poly B./TMP solution)</td>
</tr>
<tr>
<td>SULFAC® (sulfacetamide solution)</td>
</tr>
<tr>
<td>VASOCIDIN® (sulfacetamide/prednisolone solution)</td>
</tr>
</tbody>
</table>

References:

REREVIEW: OPHTHALMIC AMINOGLYCOSIDES AND COMBINATIONS

BACKGROUND

- Although bacterial conjunctivitis is generally a self-limiting condition, topical antibiotics are applied to lessen the symptoms, duration and chances of recurrence. This category will include gentamicin and tobramycin and the combinations of gentamicin/prednisolone, tobramycin/dexamethasone and tobramycin/loteprednol.
- Aminoglycosides (gentamicin and tobramycin) are broad spectrum ophthalmic antibiotics with activity against a variety of organisms including, but not limited to: *S. aureus, S. epidermidis, S. pyogenes*, some *S. pneumoniae, P. aeruginosa, E. coli, H. influenzae* and *P. mirabilis.*
• The aminoglycosides bind to the 30S ribosomal subunit of susceptible bacteria resulting in prevention of bacterial protein synthesis. Corticosteroids (prednisolone, dexamethasone and loteprednol) work by suppressing the inflammatory response to a variety of agents. Loteprednol is an analog of prednisolone resulting in slightly less elevation of intraocular pressure (IOP) compared to prednisolone. Corticosteroids slow the healing process; therefore, they should be given along with an antimicrobial agent if this delayed healing is considered to be clinically significant (e.g., when the risk of infection is high or when there is an expectation that potentially dangerous numbers of bacteria will be present in the eye).

• The aminoglycosides are indicated for the treatment of superficial ocular infections involving the conjunctiva or cornea. Tobramycin is indicated for patients over the age of 2 months and the combination of tobramycin/dexamethasone is indicated for those over 2 years. Gentamicin and its combination products do not have any specific indications based on age. The combination products are indicated for ocular conditions in which anti-inflammatory properties are needed and in which a superficial bacterial infection or risk of infection exists.

• The most common adverse effects seen with the aminoglycosides are localized ocular toxicity and hypersensitivity, lid itching, lid swelling, conjunctival erythema (less with tobramycin than with gentamicin), bacterial/fungal corneal ulcers, nonspecific conjunctivitis, conjunctival epithelial defects, and conjunctival hyperemia. The steroid component most frequently causes increased IOP. However, studies show that IOP is not increased with loteprednol (2%) to the extent that it is with prednisolone (7%). Optic nerve damage, cataract formation and delayed wound healing may occur infrequently with the use of ophthalmic corticosteroids.
  
  o Tobramycin ophthalmic ointment has been shown to produce significantly fewer adverse reactions (3.7%) than gentamicin ophthalmic ointment (10.6%) in clinical trials.
  
  o The ophthalmic steroids are contraindicated in most viral or fungal diseases of the cornea and conjunctiva as well as mycobacterial infections of the eye.
  
  o Practitioners should be warned that ophthalmic ointments may retard corneal healing. Gentamicin and the corticosteroid combination products are Pregnancy Category C; however, tobramycin is category B. Prolonged use of ophthalmic corticosteroids may cause glaucoma with damage to the optic nerve, defects in visual acuity and field of vision, cataract formation, corneal perforation and secondary ocular infection due to depression of the host immune response. Care should be taken to ensure abrupt discontinuation of the steroid combination products does not occur.

• There is very little comparative data of good quality published in the last five years regarding the products in this class.
  
  o Two hundred seventy-one patients undergoing cataract surgery in Europe and Brazil were randomized to receive tobramycin 0.3%/dexamethasone 0.1%, dexamethasone 0.1%/neomycin 0.35%/polymyxin B 6,000 units/mL, or control (neomycin 0.35%/polymyxin B 7,500 units/mL/gramicidin 20 mcg/mL) in a prospective, double-blind, parallel-group study. Results showed intraocular inflammation to be similar between the groups using tobramycin/dexamethasone and dexamethasone/neomycin/polymyxin B. Both of the corticosteroid groups had less inflammation on day 8 compared to control (p=<0.05). More allergic reactions resulting in drug withdrawal were reported with neomycin/polymyxin B/gramicidin compared with tobramycin/dexamethasone (p=<0.05).
A double-blind, randomized trial comparing tobramycin/dexamethasone and tobramycin/loteprednol in 40 patients with blepharo-keratoconjunctivitis was performed. Patients received tobramycin/dexamethasone or tobramycin/loteprednol twice daily in the test eye. After 3-5 days, the ocular surface was examined for treatment response. Results showed that tobramycin/dexamethasone significantly decreased clinical signs of ocular inflammation based on a decrease in total ocular surface scores (p=0.002), blepharitis scores (p=0.017), discharge scores (p=0.05) and conjunctivitis scores (p=0.013) compared to tobramycin/loteprednol.

- Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis should be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patients age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice.

- The AAO also recommends a course of broad spectrum antibiotics, such as tobramycin, gentamicin or cefazolin, for empiric therapy for bacterial conjunctivitis. In addition, the AAO recommends tobramycin or gentamicin for the treatment of bacterial keratitis in which the causative organism is a gram negative rod.

- In general the use of an antibiotic/corticosteroid combination drug is indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is the expectation that dangerous numbers of bacteria will be present in the eye. The AOA guidelines specifically recommend the use of topical antibiotic/steroid combinations in the treatment of herpes zoster conjunctivitis to reduce the risk of secondary bacterial infection and decrease the inflammatory response. While topical steroids are contraindicated in viral conjunctivitis, they do not exacerbate herpes zoster infections. Symptomatic patients with toxic conjunctivitis may benefit from cold compresses and/or topical ophthalmic antibiotic/corticosteroid combinations, and phlyctenular conjunctivitis responds to topical use of an antibiotic/corticosteroid combination. Again, the AOA does not name an antibiotic/corticosteroid combination of choice.

**RECOMMENDATION**

The ophthalmic aminoglycosides represent a reasonable option for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum topical antibiotics are the treatment of choice for bacterial conjunctivitis. Based on their similar spectrums of action and adverse event profiles, tobramycin and gentamicin can be considered therapeutic alternatives to one another. Antibiotic/corticosteroid combinations products are indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is an expectation that dangerous numbers of bacteria will be present in the eye. The AOA specifically recommends these combination products for the treatment of herpes zoster, toxic conjunctivitis and phlyctenular conjunctivitis. The AOA makes no differentiation between the available aminoglycosides or combination products in their guidelines. Therefore, it is recommended that at least one aminoglycoside and at least one aminoglycoside/corticosteroid combination product be available. Given that loteprednol is associated with a lower increase in IOP than other ophthalmic steroids, it should be available for those patients in whom increased IOP is a concern. In order to allow for patient and provider choice, it is recommended that there be at least one solution and one ointment dosage form available.

**COMMITTEE VOTE:**

- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION
**REREVIEW: OPHTHALMIC AMINOGLYCOSIDES AND COMBINATIONS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK-TOB (tobramycin solution)</td>
<td>GARAMYCIN® (gentamicin ointment, solution)</td>
</tr>
<tr>
<td>GENTAMICIN (Compares to Garamycin®, Genoptic®, Gentak®, Gentasol®)</td>
<td>GENOPTIC® (gentamicin ointment, solution)</td>
</tr>
<tr>
<td>PRED-G® (gentamicin/prednisolone ointment, solution)</td>
<td>GENTAK® (gentamicin ointment, solution)</td>
</tr>
<tr>
<td>TOBRAMYCIN solution (Compares to AK-Tob and Tobrex®)</td>
<td>GENTASOL® (gentamicin solution)</td>
</tr>
<tr>
<td>TOBRADEX® (tobramycin/dexamethasone ointment, solution)</td>
<td>TOBREX® (tobramycin ointment, solution)</td>
</tr>
<tr>
<td>TOBRASOL (tobramycin solution)</td>
<td>ZYLET® CC (tobramycin/loteprednol suspension)</td>
</tr>
</tbody>
</table>

**Clinical Criteria for Zylet®**

Zylet® will be approved if the recipient has a contraindication to any two of the preferred ophthalmic steroids, OR if there are concerns over a potential increase in intra-ocular pressure (IOP) with other steroids (i.e. glaucoma, recipient is pre or post cataract surgery and a known steroid-responder, etc.).

**COMMITTEE VOTE:**

APPROVED | DISAPPROVED | APPROVED with MODIFICATION

**References**

9. Rhee SS, Mah FS. Comparison of tobramycin 0.3%/dexamethasone 0.1% and tobramycin 0.3%/loteprednol 0.5% in the management of blepharo-keratoconjunctivitis. Adv Ther. 2007;24(1):60-7.
BACKGROUND

- Macrolides are broad spectrum ophthalmic antibiotics with activity against a variety of organisms including but not limited to: *H. influenzae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes* and *C. trachomatis*.

- There are two available ophthalmic macrolides, erythromycin and azithromycin. These agents are often used for the treatment of conjunctivitis and other superficial ocular infections.

- The ophthalmic macrolides prevent bacterial protein synthesis by binding to the ribosomal 50S subunit of susceptible bacteria.

- Ophthalmic azithromycin is approved for the treatment of bacterial conjunctivitis in those older than 1 year of age. Ophthalmic erythromycin is FDA-approved for the treatment of superficial ocular infections involving the conjunctiva or cornea and for prophylaxis against ophthalmia neonatorum due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in patients ranging in age from newborn to adult.

- The most common adverse effects seen with the ophthalmic macrolides include eye pain or discomfort, edema, itching and burning. Most of these reactions are associated with local irritation upon instillation; however, rarely allergic sensitization reactions such as itching, swelling and conjunctival erythema may occur. Serious hypersensitivity reactions and fungal or viral infections have been reported.

- Currently there are no head-to-head trials comparing the ophthalmic macrolides, and few comparative clinical trials exist comparing the macrolides to other ophthalmic antibiotics.
  - Azithromycin ophthalmic solution was compared to tobramycin ophthalmic solution in a prospective, randomized, active-controlled, double-masked, phase 3 trial conducted over a 14 month period at 47 sites. Patients with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to either azithromycin 1% (n=365) or tobramycin 0.3% (n=378). Rates of microbial eradication and bacterial infection recurrence were the same in both groups; however, incidence of side effects including eye irritation, conjunctival hyperemia, and worsening bacterial conjunctivitis favored the azithromycin group.
  - Azithromycin 1.5% ophthalmic solution was compared to tobramycin 0.3% ophthalmic solution in the treatment of purulent bacterial conjunctivitis. Patients (n=1043) received either 3 days of azithromycin or 7 days of tobramycin. Clinical cure rates were 87.8% for azithromycin and 89.4% for tobramycin. Both agents had comparable tolerability as well.

- Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patients age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases broad-spectrum topical antibiotics are the treatment of choice. Antibiotics can lessen the symptoms, duration and chances of recurrence.

- The AAO also recommends a course of broad spectrum antibiotics for empiric therapy for bacterial conjunctivitis. However, for treatment of chlamydial conjunctivitis, the AAO recommends azithromycin or doxycycline for adults and children >45kg. For children <45 kg, erythromycin ointment is recommended.
OPHTHALMIC AGENTS

RECOMMENDATION
The ophthalmic macrolides represent a useful class of broad-spectrum antibiotics for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum ophthalmic antibiotics are the treatment of choice for bacterial conjunctivitis; however, these guidelines fail to name an agent or class of agents of choice. Both azithromycin and erythromycin have similar spectrums of action and adverse event profiles, and thus can be considered therapeutic alternatives to one another. In order to ensure adequate patient and prescriber choice for the treatment of bacterial conjunctivitis, it is recommended that at least one ophthalmic macrolide be available. In addition, it is recommended that erythromycin ointment be available for young children and neonates with chlamydial conjunctivitis.

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

REREVIEW: OPHTHALMIC MACROLIDES

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERYTHROMYCIN ointment</td>
<td>AZASITE® (azithromycin solution)</td>
</tr>
<tr>
<td></td>
<td>ROMYCIN (erythromycin ointment)</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>

References
BACKGROUND

- There are five available quinolones for ophthalmic use, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin and ofloxacin.
- DNA gyrase is an essential enzyme involved in replication, transcription and repair of bacterial DNA. Topoisomerase IV plays a key role in the partitioning of the chromosomal DNA during bacterial cell division. The fluoroquinolones exert their antibacterial effects by inhibiting DNA gyrase and topoisomerase IV. Gatifloxacin and moxifloxacin possess an 8-methoxy substitution resulting in enhanced antimicrobial activities which may limit the selection of resistant mutants in pathogens.
- All of the ophthalmic quinolones are FDA approved for the treatment of bacterial conjunctivitis. Ciprofloxacin solution, levofloxacin 1.5% solution and ofloxacin are also indicated for the treatment of corneal ulcers. All products, with the exception of ciprofloxacin ointment (≥ 2 years), are approved in children one year or older.
- The susceptibilities of the ophthalmic quinolones vary slightly among the different agents.
  - In general, all quinolones provide excellent activity against the most frequent ophthalmic pathogens including *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Streptococcus pneumoniae*, *Streptococcus viridans* and *Pseudomonas aeruginosa*.
  - Ciprofloxacin exhibits greater gram-negative activity than the other quinolones.
  - The fourth-generation agents (moxifloxacin and gatifloxacin) exhibit greater activity against gram positive organisms as well as against second-generation fluoroquinolone resistant pathogens (especially *S. aureus*).
    - Among the fourth generation quinolones, moxifloxacin exhibits better gram-positive coverage while gatifloxacin exhibits better gram-negative coverage.
- The most common adverse effects associated with the ophthalmic quinolones include pain or discomfort, edema, foreign body sensation, itching, conjunctival hyperemia and transient burning. Most of these reactions are associated with local irritation upon instillation; however, rarely allergic sensitization reaction such as itching, swelling and conjunctival erythema may occur. Serious hypersensitivity reactions and fungal or viral infections have been reported.
- Several head-to-head clinical trials have been performed to compare the ophthalmic quinolones.
  - Gatifloxacin 0.3% was compared to ciprofloxacin 0.3% in a randomized, double-masked trial of 104 eyes of 104 patients with bacterial keratitis. The majority of pathogens identified were gram-positive. Results showed significantly more patients in the gatifloxacin group had complete healing compared to those in the ciprofloxacin group (p=0.042). In vitro results demonstrated gatifloxacin was more effective against gram positive cocci (p=<0.001) and produced significantly faster healing rates in patients with gram-positive pathogens (p=0.009). For gram-negative bacteria, the mean healing time and efficacy were similar in both treatment groups.
  - Patients (n=167) ages 1-16 years were given either levofloxacin 0.5% or ofloxacin 0.3% every 2 hours on days 1 and 2 and every 4 hours on days 3-5 for the treatment of bacterial conjunctivitis. At the study endpoint (mean of 6.5 days), levofloxacin demonstrated greater microbial eradication than ofloxacin (p=≤ 0.032) for children ages 2-11 years only.
A double-blind, randomized, prospective trial compared healing rates among 35 patients who received moxifloxacin in one eye and gatifloxacin in the other eye following photorefractive keratectomy (PKR). Both eyes healed on the same day in 18 patients (51.4%), while the moxifloxacin-treated eye healed first in 13 patients (37.1%) and the gatifloxacin-treated eye healed first in 4 patients (11.4%). The median healing time for both agents was 4 days (range 3-7 days for moxifloxacin, 3-9 days for gatifloxacin); however, only 69% of gatifloxacin treated eyes had healed by day 4 compared to 80% of moxifloxacin-treated eyes (p=0.001).

An open-label study involving 46 patients undergoing corneal transplant compared healing rates of moxifloxacin versus gatifloxacin. Results showed that gatifloxacin was associated with smaller epithelial defects at days 4 and 7 compared to moxifloxacin (p=<0.001). In addition, more eyes showed complete reepithelialization of the corneal graft with gatifloxacin after day 4 (statistically significant at days 7 and 14) than with moxifloxacin.

- Unlike the other agents in this class, moxifloxacin does not contain a preservative and it is only administered three times daily for conjunctivitis.
- Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patient’s age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice. Antibiotics can lessen the symptoms, duration and chance of recurrence. The AAO recommends topical broad-spectrum antibiotics to be used initially in the empiric treatment of bacterial keratitis. The initial therapeutic regimen should be modified when the eye shows a lack of improvement or stabilization within 48 hours.

RECOMMENDATION
Despite the slight differences in FDA-approved indications, all products in this class can be used to treat ophthalmic infections involving the conjunctiva or cornea which are caused by susceptible bacteria. The fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin) may provide better coverage for gram-positive and resistant organisms than the third generation (levofloxacin) and second generation (ciprofloxacin and ofloxacin) products. According to current treatment guidelines from the AOA, broad-spectrum topical antibiotics are the treatment of choice in most cases of bacterial conjunctivitis diagnosed without culture or smear. The AAO also recommends broad-spectrum topical antibiotics as initial therapy for the treatment of bacterial keratitis. Neither group suggests one agent over another. Therefore it is recommended that at least two products be available, one of which should be a fourth-generation agent.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: OPHTHALMIC ANTIBIOTICS, QUINOLONES

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPROFLOXACIN SOLUTION</td>
<td>CILOXAN® QC (ciprofloxacin solution and ointment)</td>
</tr>
<tr>
<td>(Compared to Ciloxan)</td>
<td>IQUIX® (levofloxacin 1.5% solution)</td>
</tr>
<tr>
<td>VIGAMOX® SOLUTION (moxifloxacin)</td>
<td>OCUFLOX® (ofloxacin solution)</td>
</tr>
<tr>
<td></td>
<td>OFLOXACIN (Compared to Ocuflox solution)</td>
</tr>
<tr>
<td></td>
<td>QUIXIN® (levofloxacin 0.5% solution)</td>
</tr>
<tr>
<td></td>
<td>ZYMAR® (gatifloxacin solution)</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION
OPHTHALMIC NSAIDS

BACKGROUND

- Ophthalmic NSAIDs are most commonly used for ophthalmic surgery. These agents have utility to reduce pain and control inflammation during and after surgery as well as to maintain pupillary dilatation during surgery without a significant effect on IOP.

- The ophthalmic NSAIDs exert their anti-inflammatory and analgesic effects through the ability to inhibit prostaglandin biosynthesis in the eye. Prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased IOP. Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter.

- FDA approved indications:
  - Bromfenac, diclofenac and nepafenac are indicated for the treatment of postoperative inflammation and pain secondary to cataract extraction. Diclofenac has an additional indication for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
  - Flurbiprofen is indicated for the inhibition of intraoperative miosis.
  - Ketorolac 0.5% is indicated for the treatment of post-operative inflammation secondary to cataract extraction as well as temporary relief of ocular itching due to allergic conjunctivitis.
  - Ketorolac 0.4% is indicated for the reduction of ocular pain, burning and stinging after corneal refractive surgery.
  - Ketorolac 0.5% preservative-free is indicated for the reduction of ocular pain and photophobia secondary to incisional refractive surgery.

- Common adverse effects associated with the use of ophthalmic NSAIDs include:
  - Instillation reactions, corneal edema, and vision changes.

- Continued use of topical NSAIDs may result in severe corneal adverse events, including: corneal thinning, erosion, ulceration or perforation, which may become sight damaging. Therefore, the use of ophthalmic NSAIDs beyond 14 days is not recommended.
OPHTHALMIC AGENTS

- Bromfenac contains sodium sulfite and is contraindicated in patients with sulfite hypersensitivity.
- All agents in this class are Pregnancy Category C.
- Due to the topical administration of the ophthalmic NSAIDs, systemic absorption is minimal; therefore, clinically significant drug interactions are not well defined.
- There are several head to head trials comparing the ophthalmic NSAIDs.
  - Three trials compared diclofenac and ketorolac 0.5% for efficacy and tolerability in a total of 150 post-ocular surgery patients. No difference was found in any of the trials with regards to anti-inflammatory effects or reduction of ocular pain. Adverse effects, including instillation reactions and the incidence of post-operative posterior opacification, were similar between the treatment groups.
  - Ketorolac 0.4% and nepafenac were compared in a randomized, double-blind study of 132 patients undergoing cataract surgery. More patients receiving ketorolac had ocular PGE (2) levels below the level of detection than those receiving nepafenac (61.9% vs, 17.5%, p<0.001). Additionally, active drug concentrations in the eye were significantly higher with ketorolac than with amfenac, the active drug of nepafenac (p<0.001).
- In addition, there are several trials available comparing ophthalmic NSAIDs to ophthalmic steroids post-cataract surgery. In general, the literature shows that NSAIDs provide similar inflammatory control and superior pain control than steroids.
  - One randomized, double-blind study compared prednisolone 1%, rimexolone 1%, and ketorolac 0.5% among 45 patients undergoing cataract extraction. Patients were assigned to one of the topical treatments post-surgery, and assessed for inflammation, best-corrected visual acuity, and IOP. The efficacy of inflammation control did not differ among the treatment groups (p=0.165), nor did visual acuity. However, one patient developed increased IOP with prednisolone, and one patient developed a corneal ulcer with ketorolac.
  - Another randomized, double-blind trial compared ketorolac 0.5%, diclofenac 0.1%, and prednisolone acetate 1% among 58 patients undergoing cataract surgery. No statistically significant differences were observed in flare, cell counts, or intraocular pressure.
  - A randomized trial involving 40 pediatric patients undergoing strabismus surgery compared topical diclofenac 0.1% to dexamethasone 0.1%. By week 2 post-surgery, patients in the diclofenac group reported less discomfort and had less conjunctival inflammation, edema, and gap than patients in the dexamethasone group (p<0.05). At 4 weeks post-surgery, the difference in patient discomfort and conjunctival gap remained significant. In addition, by 4 weeks post-op, 38% of patients in the dexamethasone group had developed increased IOP, while no increase in IOP was seen in the diclofenac group.
  - A randomized trial comparing involving 37 patients undergoing posterior segment surgery compared topical diclofenac to dexamethasone. Patients receiving diclofenac reported lower pain scores at days 1 and 15 than those receiving dexamethasone (p<0.05).

- Guidelines from the AAO regarding surgical management of cataracts state that there is no established optimal post-operative regimen of topical antibiotics, steroids, and NSAIDs. Therefore, they recommend that it should be the decision of the operating surgeon to use any or all of these products singly or in combination. The AAO guidelines point out that there is no difference in rates of post-capsular opacification (the most common problem encountered post-cataract surgery) between topical steroids and topical NSAIDs. Importantly, the guidelines point out that there is evidence that NSAIDs alone or in combination with steroids are more effective than steroids alone at preventing cystoid macular edema (CME), a serious sight-threatening complication of cataract surgery.
In general, ophthalmic corticosteroids are widely considered first line therapy for the treatment of ophthalmic inflammatory conditions but are commonly associated with increased IOP, which may place some patient populations at risk, including glaucoma patients. Immunosuppressed patients and patients with concerns for wound healing should also avoid the use of corticosteroids. Ophthalmic NSAIDs offer the anti-inflammatory benefits without the risks associated with ophthalmic corticosteroids.

RECOMMENDATION
Ophthalmic NSAIDs are most commonly used for the treatment of inflammation and pain secondary to ophthalmic surgery. Although there are no clinical guidelines which address the appropriate use of ophthalmic NSAIDs, ophthalmic corticosteroids are widely considered first line therapy for the treatment of ophthalmic inflammatory conditions. However, due to adverse effects, certain patient populations should avoid the use of corticosteroids. Ophthalmic NSAIDs offer the anti-inflammatory benefits without the risks associated with ophthalmic corticosteroids in these patient populations. Guidelines from the AAO regarding ophthalmic surgery recommend ophthalmic NSAIDs as an alternative to or in combination with ophthalmic corticosteroids for the treatment of ophthalmic inflammation associated with cataract surgery. The AAO guidelines do not distinguish between the various NSAIDs for use post-cataract surgery. Based on all of this information, it appears that the ophthalmic NSAIDs produce similar anti-inflammatory and pain relieving effects and can thus be considered therapeutic alternatives to one another. In order to maintain costs and ensure appropriate use, it is recommended that ophthalmic NSAIDs be reserved for patients for whom corticosteroid monotherapy is not appropriate.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: OPHTHALMIC NSAIDS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLURBIPROFEN® ST (compares to Ocufen®)</td>
<td>DICLOFENAC® ST (compares to Voltaren®)</td>
</tr>
<tr>
<td>ACULAR® ST (ketorolac)</td>
<td>NEVANAC® ST (nepafenac)</td>
</tr>
<tr>
<td>ACULAR® LS ST (ketorolac)</td>
<td>OCUFEN® ST (flurbiprofen)</td>
</tr>
<tr>
<td>ACULAR® PF ST (ketorolac, preservative-free)</td>
<td>VOLTAREN® ST (diclofenac)</td>
</tr>
<tr>
<td>XIBROM® ST (bromfenac)</td>
<td></td>
</tr>
</tbody>
</table>

Class Step Therapy
Recipients will be approved for an ophthalmic NSAID if any of the following are true:
1. The recipient is using the ophthalmic steroid for pain pre- or post-ocular surgery
2. The recipient has a contraindication, intolerance or adverse reaction to an ophthalmic steroid (i.e. prednisolone, dexamethasone, fluorometholone, etc.). Acceptable reasons for not using an ophthalmic steroid include, but are NOT limited to:
   - Concerns that a potential increase in intraocular pressure (IOP) with ophthalmic steroids would place patient at risk (i.e., glaucoma, pre-/post-cataract surgery, etc.)
   - Concerns that the steroid would impair wound healing
   - Concerns that the steroid may cause/induce infection due to immunosuppression.
3. Concomitant use of an ophthalmic steroid and an ophthalmic NSAID is needed to control inflammation

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION
OPHTHALMIC AGENTS

References
5. el-Harazi SM, et al. A randomized double-masked trial comparing ketorolac tromethamine 0.5%, diclofenac sodium 0.1%, and prednisolone acetate 1% in reducing post-phacoemulsification flare and cells. Ophthalmic Surg Lasers. 1998; 29(7): 539-44.
LENGTH OF AUTHORIZATIONS:  Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

Acceptable reasons include:

- **Allergy** to medications not requiring prior approval
- **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
- **History** of unacceptable/toxic side effects to medications not requiring prior approval

The requested medication may be approved if both of the following are true:

- If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
- The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

The requested medication may be approved if the following is true:

- An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class within the Renal/Genitourinary Agents is organized into the following sections when applicable:

**BACKGROUND:**
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

**RECOMMENDATION:**
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)
BACKGROUND

- Overactive bladder (OAB) is generally associated with spastic contractions of the detrusor muscle and characterized by urinary urgency with or without urge incontinence usually combined with urinary frequency and nocturia. This is a chronic and debilitating syndrome which can result in significant changes to a patient’s quality of life. Overactive bladder may be caused by: lower urinary tract conditions such as urinary tract infection or obstruction; neurological conditions such as stroke or Alzheimer’s disease; systemic conditions such as heart failure or vascular insufficiency; functional or behavioral conditions such as impaired mobility and various medications such as diuretics or narcotics.

- The major peripheral neurotransmitter responsible for bladder contraction is acetylcholine which works by interacting with muscarinic receptors on the detrusor muscle. There are five known muscarinic receptor subtypes. Subtypes M₂ and M₃ are associated primarily with bladder activity with M₃ being primarily responsible for normal micturition. The M₂ and M₃ muscarinic receptor subtypes are also involved in contraction of gastrointestinal smooth muscle, saliva production, and iris sphincter function. The antimuscarinic drugs depress both voluntary and involuntary bladder contractions resulting in increased residual urine and incomplete emptying of the bladder and consequently a decrease in detrusor pressure.

- Flavoxate is a synthetic urinary tract antispasmodic agent that prevents urinary tract smooth muscle spasms possibly through phosphodiesterase inhibition or calcium antagonistic activity. The other agents in this class all exert their effects by interacting with the muscarinic receptors.
  - Oxybutynin is a potent, nonselective, antimuscarinic drug which exerts most of its effects on the M₃ receptors. Because it is nonselective, oxybutynin may produce side effects consistent with anticholinergic actions in the CNS, parotid gland and GI tract.
  - Tolterodine and its active metabolite, 5-hydroxymethyltolterodine, are competitive muscarinic receptor antagonists; however, they show selectivity for the urinary bladder resulting in limited CNS activity.
  - Trospermium is an antimuscarinic agent that has high affinity to the M₁, M₂, and M₃ receptor subtypes. Trospermium is a hydrophilic quaternary amine; therefore, it does not cross the blood-brain barrier or conjunctiva resulting in reduced risk of CNS-related side effects such as sedation and dizziness.
  - Darifenacin selectively antagonizes M₃ muscarinic receptors in the bladder.
  - Solifenacin is a competitive M₃-selective muscarinic receptor antagonist with functional selectivity for the bladder, but it has some effect on all muscarinic receptors. Solifenacin also has poor CNS penetration resulting in minimal CNS side effects.

- Flavoxate is indicated for the symptomatic relief of dysuria, urinary frequency and urgency, nocturia, suprapubic pain and incontinence associated with cystitis, prostatitis, urethritis or urethrocyctitis/urethrotogonitis. Darifenacin, oxybutynin ER, oxybutynin transdermal, solifenacin, tolterodine IR/ER and trospermium are all FDA approved for the treatment of overactive bladder which results in urge urinary incontinence, urgency and frequency. Oxybutynin ER has an additional indication for the treatment of pediatric patients ≥ 6 years old with symptoms of detrusor over activity associated with neurological conditions such as spina bifida. Oxybutynin IR is approved in those ≥ 5 years old for the relief of symptoms of bladder instability associated with voiding (urgency, frequency, urinary leakage, urge incontinence, dysuria) in patients with uninhibited neurogenic or reflex neurogenic bladder.
• Flavoxate is most commonly associated with GI upset, xerostomia, headache, somnolence, blurred vision, nervousness and pharyngeal dryness. All other agents in this class have varying rates of adverse events depending on their specificity for muscarinic receptors in the bladder or abilities to penetrate the blood-brain barrier.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Constipation</th>
<th>Diarrhea</th>
<th>Dry Mouth</th>
<th>Dyspepsia</th>
<th>Dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>darifenacin</td>
<td>21.3</td>
<td>0.9</td>
<td>35.3</td>
<td>8.4</td>
<td>1.3</td>
</tr>
<tr>
<td>oxybutynin</td>
<td>12.6</td>
<td>5.0</td>
<td>71.4</td>
<td>7.0</td>
<td>15.6</td>
</tr>
<tr>
<td>oxybutynin ER</td>
<td>13</td>
<td>9</td>
<td>61</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>oxybutynin transdermal**</td>
<td>3.3</td>
<td>3.2</td>
<td>9.6</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>solifenacin</td>
<td>13.4</td>
<td>nr</td>
<td>27.6</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>tolterodine</td>
<td>7</td>
<td>4</td>
<td>35</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>tolterodine ER</td>
<td>6</td>
<td>nr</td>
<td>23</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Trospium</td>
<td>9.6</td>
<td>nr</td>
<td>20.1</td>
<td>1.2</td>
<td>nr</td>
</tr>
</tbody>
</table>

**May also cause mild application site reactions such as erythema (5-40%) or itching (14-17%).

- Flavoxate is contraindicated in patients with achalasia, gastrointestinal hemorrhage, obstructive intestinal lesions or ileus, obstructive uropathy or pyloric or duodenal obstruction. All other agents in this category are contraindicated in patients with uncontrolled narrow-angle glaucoma and gastric or urinary retention.

- Flavoxate should be used with caution in those patients with suspected glaucoma. Solifenacin and tolterodine require dosage adjustments in hepatic and renal impairment. Caution should be used when patients with hepatic and renal insufficiency are treated with oxybutynin or trospium; however, there are no specific dosing recommendations. Trospium also requires dosage adjustment in renal impairment and elderly patients. Darifenacin should be used cautiously in patients with hepatic dysfunction; however, no specific recommendations regarding appropriate dosing exists. Due to the anticholinergic effects of darifenacin, oxybutynin and trospium, they should be used cautiously in patients with Myasthenia gravis and ulcerative colitis. In addition, darifenacin should be used cautiously in patients with severe constipation, prostatic hypertroph or xerostomia due to its anticholinergic activities. Solifenacin and tolterodine should also be used cautiously in those patients with a history of prolonged QT interval or concomitant use of drugs which may prolong QT interval. Agents in this class are Pregnancy Category C with the exception of flavoxate and oxybutynin (B).

- All of these agents, with the exception of trospium and flavoxate, are metabolized by the cytochrome P450 enzyme system through varying substrates leading to multiple potential drug-drug interactions.

- There have been multiple head-to-head trials comparing the urinary tract antispasmodics in the adult population; however, these trials have failed to determine a superior agent when it comes to efficacy. On the other hand, these trials have shown that the newer agents improve quality of life in women with overactive bladder and urinary incontinence with a smaller incidence of anticholinergic side effects. However, these newer agents have not been compared with extended-release formulations of tolterodine or oxybutynin which are better tolerated than the immediate-release versions.
RARELY DO WE SEE HEAD-TO-HEAD PLACEBO-CONTROLLED TRIALS IN CHILDREN; HOWEVER, SUCH A TRIAL WAS CONDUCTED COMPARING OXYBUTYNIN ER TO TOLTERODINE IR AND ER. OXYBUTYNIN IR AND OXYBUTYNIN ER ARE THE ONLY AGENTS IN THIS CLASS WITH AN FDA APPROVED INDICATION FOR PEDIATRIC PATIENTS WITH SYMPTOMS OF DETRUSOR ACTIVITY ASSOCIATED WITH NEUROLOGICAL CONDITIONS.

- Children (n=132) with a history of diurnal urinary incontinence were randomly assigned to oxybutynin ER, tolterodine IR, or tolterodine ER with dosage titration to effect, maximum recommended dose or intolerable side effects. Oxybutynin ER and tolterodine ER were superior for reducing daytime urinary incontinence compared to tolterodine IR (p<0.01 and p<0.05, respectively). Oxybutynin ER was more effective than tolterodine ER for complete resolution of diurnal incontinence (p<0.05).

- The 2005 guidelines from the Finnish Medical Society recommend oxybutynin for patients with mild urge incontinence. They recognize that the new slow release formulation of oxybutynin causes fewer side effects. The 2006 guidelines from the National Institute for Health and Clinical Excellence states that first line therapy for women with OAB or urinary incontinence should be immediate release non-proprietary oxybutynin if bladder training has been ineffective. Darifenacin, solifenacin, tolterodine, trospium, or an extended release or transdermal formulation of oxybutynin are considered second line therapy. These guidelines further state that there is no evidence of a clinically important difference in efficacy among the antimuscarinic drugs. Adverse effects are common with all antimuscarinic drugs, and dry mouth is more common with immediate release oxybutynin. However, skin reactions are more common with tolterodine, trospium and extended release or transdermal oxybutynin.

RECOMMENDATION
The agents in this class can all improve the quality of life for those patients with urinary incontinence, urgency and frequency. Flavoxate is generally only used short term during the treatment of acute cystitis, prostatitis, urethritis or urethrocystitis/urethrotgonitis. The other agents in this category are used specifically for the long term treatment of overactive bladder. The urinary tract antispasmodics have all been shown to provide similar efficacy; however, they appear to differ in their potential for anticholinergic effects and drug-drug interactions. In addition, oxybutynin is the only agent in the category with an FDA approved indication for pediatric patients as young as 5 years old. Therefore, it is recommended that at least three agents be available, at least one of which should be a selective antagonist of muscarinic receptors in the bladder and one of which should be oxybutynin.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>REREVIEW: URINARY TRACT ANTISPASMODICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>ENABLEX® QL (darifenacin)</td>
</tr>
<tr>
<td>DETROL LA® QL (tolterodine)</td>
</tr>
<tr>
<td>FLAVOXATE (Compares to Urispas®)</td>
</tr>
<tr>
<td>OXYBUTYNIN (Compares to Ditropan®)</td>
</tr>
<tr>
<td>VESICARE® QL (solifenacin)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
## RENAL/GENITOURINARY AGENTS

### Quantity Limits

<table>
<thead>
<tr>
<th>Medication</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrol®</td>
<td>2/day</td>
</tr>
<tr>
<td>Detrol® LA</td>
<td>1/day</td>
</tr>
<tr>
<td>Ditropan® XL 5 mg</td>
<td>1/day; 10 mg, 15 mg = 2/day</td>
</tr>
<tr>
<td>Enablex®</td>
<td>1/day</td>
</tr>
<tr>
<td>Oxybutynin ER 5 mg</td>
<td>1/day; 10 mg, 15 mg = 2/day</td>
</tr>
<tr>
<td>Oxytrol®</td>
<td>8 patches/26 days</td>
</tr>
<tr>
<td>Sanctura®</td>
<td>2/day</td>
</tr>
<tr>
<td>VESIcare®</td>
<td>1/day</td>
</tr>
</tbody>
</table>

### COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>Vote</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROVED</td>
<td>DISAPPROVED</td>
</tr>
<tr>
<td>APPROVED with MODIFICATION</td>
<td></td>
</tr>
</tbody>
</table>

### References


### REREVIEW: ANDROGEN HORMONE INHIBITORS

#### BACKGROUND

- Testosterone that is converted to 5α-dihydrotestosterone (DHT) is a key element in the pathophysiology of BPH, because it stimulates the growth of glandular and stromal cells which over time results in increased prostate size and bladder outlet obstruction. The 5α-reductase inhibitors (5ARs) prevent the conversion of testosterone to DHT resulting in a decline in proliferation of prostatic epithelial cells and a decrease in prostate size. The type II isoenzyme is primarily active in the reproductive tissues where as type I is responsible for testosterone conversion in the skin and liver. Dutasteride inhibits both type I and type II isoforms of 5α-reductase while finasteride only inhibits the type II isoform.
- All of the 5ARs are FDA-approved for the symptomatic treatment of BPH.
- The most common adverse reactions seen with the 5ARs are impotence, altered libido, dizziness, abnormal ejaculation, asthenia, hypotension and headache.
  - Women who are pregnant or may become pregnant should not come into contact with 5ARs. These agents may be absorbed through the skin and cause abnormalities in the external genitalia of a male fetus; therefore, the 5ARs are Pregnancy Category X.
5ARs should be used with caution in men with obstructive uropathy or abnormal liver function. Prostate carcinoma should be ruled out before initiation of a 5AR. The 5ARs reduce total serum prostate specific antigen (PSA) concentration by approximately 40% following 3 months of treatment and 50% following 6, 12 and 24 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs a new baseline PSA concentration should be established after 3 to 6 months of treatment, and this new value should be used to assess potentially cancer-related changes in PSA.

There have been no head to head trials comparing the 5AR agents. However, one study has been completed comparing combination therapy with an alpha blocker plus a 5AR to the single agents or placebo.

The NIH-funded Medical Therapy of Prostatic Symptoms (MTOPS) study enrolled 3,047 men with moderate or severe symptomatic BPH in a long-term (4.5 years), double-blind trial. Participants were randomized to receive placebo, doxazosin (4-8 mg), finasteride (5 mg) or a combination of doxazosin plus finasteride. Seventeen percent of men treated with placebo, 10% of those treated with doxazosin (p=0.001 versus placebo), 10% of men treated with finasteride (p=0.002 versus placebo) and 5.3% of those treated with combination therapy (p=<0.001 compared to each of the other treatments) experienced clinical BPH progression defined as symptom increase, urinary retention, urinary incontinence, renal insufficiency or recurrent urinary tract infection. Acute urinary retention (p=<0.001) and invasive therapy (p=<0.001) were significantly reduced by combination therapy when compared with placebo. Finasteride monotherapy also showed a significant reduction (p=<0.001) in acute urinary retention and invasive therapy compared to placebo; however, doxazosin monotherapy did not show this reduction. The overall lower rate of urinary retention and invasive therapy, at least in part, may be attributed to the fact that patients in this study had smaller prostate glands on average than patients in most other studies. Discontinuation rates were 27% for doxazosin, 24% for finasteride and 18% for combination therapy.

A follow up study looked at the relationship between baseline total prostate volume (TPV) and the effect of medical therapy among patients enrolled in the MTOPS study. Results showed that in men with a small prostate (baseline TPV <25 mL) combination therapy was no better than doxazosin alone for decreasing the risk of clinical progression of BPH and the need for invasive therapy. However, in men with a moderate size (25-40 mL) or enlarged (≥40 mL) prostate gland, combination therapy led to a greater decrease in the risk of clinical progression of BPH than either drug alone.

The 2003 American Urology Association (AUA) guidelines for the management of BPH recommend watchful waiting for patients with mild symptoms of BPH which do not interfere with daily life. It is also an appropriate option for men with moderate to severe symptoms who have not yet developed complications of BPH such as renal insufficiency, urinary retention or recurrent infection. These guidelines recommend the 5ARs for patients with LUTS associated with demonstrable prostatic enlargement, but do not recommend these agents for men with LUTS who do not have evidence of prostatic enlargement. Patients with symptomatic prostatic enlargement but without LUTS may be offered 5ARs to prevent the progression of the disease; however, patients should be warned about the adverse effects (such as sexual dysfunction) and the potential for disease progression so that an informed decision about treatment can be made. The guidelines do not recommend one 5AR over another and state that finasteride and dutasteride display similar efficacy and comparable safety profiles. The AUA guidelines recommend the combination of an alpha blocker and a 5AR for patients with LUTS associated with demonstrable prostatic enlargement. However, MTOPS has raised the question about whether those men with moderate prostate enlargement may benefit from combination therapy. More studies are underway which will help to answer the question about appropriate candidates for combination therapy.
RECOMMENDATION
The 5α-reductase inhibitors (5ARs) prevent the conversion of testosterone to DHT resulting in a decline in proliferation of prostatic epithelial cells and decreased prostate size. Current treatment guidelines from the AUA recommend the 5ARs (either as monotherapy or in combination with alpha blockers) for patients with LUTS associated with demonstrable prostatic enlargement. These guidelines make no differentiation among the available agents. Therefore, these agents can be considered therapeutic alternatives to one another, and it is recommended that at least one agent be available.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

REREVIEW: ANDROGEN HORMONE INHIBITORS

PREFERRED | NON-PREFERRED
---|---
PROSCAR® QL (finasteride) | AVODART® QL (dutasteride)
FINASTERIDE QL (compares to Proscar®)

Quantity Limits
Avodart®: 1/day
finasteride: 1/day
Proscar®: 1/day

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

References
BACKGROUND

- Symptoms of benign prostatic hyperplasia (BPH) are caused by hyperplastic changes in the prostate tissue resulting in prostate enlargement. This obstruction causes increased urinary outflow resistance and an impaired detrusor muscle response. While not fully understood, the initial hyperplastic changes may be the result of hormonal changes. Patients with BPH may present with lower urinary tract symptoms (LUTS) as a result of irritation (urinary frequency, nocturia, urgency, urge, incontinence) and/or obstruction (difficulty initiating urination or passing urine, weak stream, involuntary postvoid dripping of urine or sensation of incomplete bladder emptying). BPH is more likely to occur in men over 60 years of age. Severe BPH can lead to urinary retention, renal insufficiency, urinary tract infections, hematuria and bladder stones. Uremia and irreversible bladder dysfunction are possible but less likely to occur.

- Unlike a normal prostate, the prostate of a man with BPH has a higher ratio of stromal to glandular tissue. Prostatic smooth muscle is innervated by $\alpha_1$- and $\alpha_2$-adrenergic receptors. The outer prostatic capsule, bladder neck and proximal urethra have a high concentration of $\alpha_1$-adrenergic receptors as well. Excessive stimulation of the $\alpha_1$-adrenergic receptors causes the smooth muscle of the prostate, prostatic capsule, bladder neck, and proximal urethra to contract resulting in a decrease in the urethral lumen and obstructive voiding symptoms such as difficulty in urination, decreased force of urinary stream, urinary hesitancy, straining to void, incomplete bladder emptying, urinary dribbling and intermittent urinary stream.

- The alpha blockers (tamsulosin, alfuzosin, terazosin and doxazosin) relax both the bladder neck and prostate smooth muscle resulting in decreased pressure in the bladder and urethra, thereby improving urinary flow. Because of their mechanism of action, these agents are more effective at improving obstructive symptoms than irritative symptoms. Tamsulosin and alfuzosin have a higher affinity and selectivity for $\alpha_1A$-adrenergic receptors that are located in the nonvascular smooth muscle of the prostate. These highly selective properties may result in a decreased incidence of adverse cardiovascular effects.

- All of the alpha blockers are indicated for the symptomatic treatment of BPH.

- The most common adverse reactions observed with alpha blocker use are headache, abnormal ejaculation, dizziness, altered libido, asthenia, orthostatic hypotension or impotence. Priapism, leading to permanent impotence if not properly treated, is a rare but severe adverse reaction which may occur with alpha blocker treatment.
  - The FDA has issued a black box warning for doxazosin and terazosin regarding syncope and a potential “first-dose” hypotension and/or syncope. These adverse effects are especially bothersome if these agents are given in conjunction with other antihypertensive drugs.
  - All agents in this class should be used with caution in patients with hepatic insufficiency. Alfuzosin is contraindicated in patients with moderate or severe hepatic insufficiency (Childs Pugh B or C).
  - Carcinoma of the prostate should be ruled out before initiation of an alpha blocker.
  - It is recommended that male patients being considered for cataract surgery be screened for alpha blocker usage. Intraoperative floppy iris syndrome (IFIS) has been reported following cataract surgery in some patients taking alpha blockers, either concurrently or recently.
  - Doxazosin should be used with caution in the elderly as the incidence for hypotension seems to increase with age.
Multiple head to head trials have been performed using the alpha blockers as treatment for BPH. These trials have failed to identify a superior agent in the class. Selective alpha-blockers (alfuzosin and tamsulosin) have decreased incidence of hypotension; therefore, they have been identified as safer agents compared to the non-selective alpha-blockers.

The 2003 American Urology Association (AUA) guidelines for the management of BPH recommend watchful waiting for patients with mild symptoms of BPH which do not interfere with daily life. It is also an appropriate option for men with moderate to severe symptoms who have not yet developed complications of BPH such as renal insufficiency, urinary retention or recurrent infection. These guidelines state that all of the alpha blockers are appropriate treatment for patients with LUTS secondary to BPH. The AUA does not differentiate between agents regarding clinical efficacy; however, they do recognize that adverse event profiles vary slightly. The AUA guidelines recommend the combination of an alpha blocker and a 5α-reductase inhibitor for patients with LUTS associated with demonstrable prostatic enlargement.

RECOMMENDATION
The alpha-blockers have been shown to significantly increase urinary flow rates and decrease outflow obstruction and irritation symptoms, such as frequency, nocturia, urgency and urge incontinence associated with benign prostatic hyperplasia (BPH). Because alfuzosin and tamsulosin are highly selective for the alpha receptors in the genitourinary tract compared to the vasculature, it is reasonable to prefer them due to their potential for reduced cardiovascular side effects such as orthostatic hypotension and first-dose syncope. The AUA recommends alpha blockers for men with LUTS secondary to BPH. The AUA does not differentiate between agents regarding clinical efficacy; however, they do recognize that adverse event profiles vary slightly. Therefore, it is recommended that at least two alpha blockers be available. In addition, it is recommended that, of the preferred agents, at least one should be highly selective for the alpha receptors in the genitourinary tract.

COMMITTEE VOTE:

APPROVED      DISAPPROVED      APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOXAZOSIN (Compares to Cardura®)</td>
<td>CARDURA® (doxazosin)</td>
</tr>
<tr>
<td>FLOMAX® QL (tamsulosin)</td>
<td>CARDURA XL® QL (doxazosin extended release)</td>
</tr>
<tr>
<td>TERAZOSIN (Compares to Hytrin®)</td>
<td>HYTRIN® (terazosin)</td>
</tr>
<tr>
<td>UROXATRAL® QL (alfuzosin)</td>
<td></td>
</tr>
</tbody>
</table>

Quantity Limits
Cardura XL® 4 mg: 1/day
8 mg: 1/day
Flomax®: 2/day
Uroxatral®: 1/day

COMMITTEE VOTE:

APPROVED      DISAPPROVED      APPROVED with MODIFICATION
References