Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

August 14, 2007
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.

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\(^1\) 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 Cardiovascular Agents is organized into the following sections when applicable:

BACKGROUND:
- General overview
- Pharmacology
- Therapeutic effect(s) (i.e., blood pressure lowering, lipid lowering, etc.)
- 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)
NEW: ANTI-ANGINAL AGENTS – MISCELLANEOUS

BACKGROUND

- Ranexa® (ranolazine) is indicated for the treatment of chronic angina; however, because ranolazine prolongs the QT interval, its use should be reserved for individuals who have not achieved an adequate response on other anti-anginal drugs. Ranolazine should be used in conjunction with amlodipine, beta-blockers, or nitrates.
- Ranolazine produces its anti-anginal and anti-ischemic effects by reducing sodium entry into myocardial cells through sodium channels that either fail to inactivate or that reopen. As a result, calcium uptake via the sodium/calcium exchanger is reduced.
- Common adverse events associated with ranolazine include dizziness, headache, constipation, and nausea. Ranolazine is contraindicated in patients with pre-existing QT prolongation, hepatic function impairment, receiving QT-prolonging drugs, or on potent or moderately potent CYP3A inhibitors, including diltiazem.
- A few large trials have investigated the use of ranolazine in chronic angina.
  - The Efficacy of Ranolazine In Chronic Angina (ERICA) trial enrolled 565 adults with stable coronary disease and ≥3 angina attacks per week and randomized them to receive either ranolazine (n=281) or placebo (n=284). Compared with placebo, ranolazine significantly reduced angina frequency and nitroglycerin consumption.
  - The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial assessed the impact of ranolazine vs. placebo on exercise tolerance and angina frequency in 823 adults with severe chronic angina who were already taking standard doses of atenolol, amlodipine, or diltiazem. This study found that twice-daily doses of ranolazine increased exercise capacity and reduced angina frequency compared to placebo.
- The ACC/AHA Guidelines for Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease recommend combination therapy with a beta-blocker, aspirin (or clopidogrel), a statin, and an ACE inhibitor (in pts with CAD, diabetes, and/or LV systolic dysfunction); long-acting nitrates or calcium channel blockers are recommended when beta-blockers are contraindicated or unsuccessful. Ranexa® is not included in the ACC/AHA guidelines for angina.

RECOMMENDATION

Given the limited clinical trials available and the risk of QT interval prolongation, it is recommended that Ranexa® be reserved for patients with chronic angina who have not achieved an adequate response on beta-blockers, long-acting nitrates, and/or calcium channel blockers. To ensure appropriate use, it is recommended that Ranexa® be subject to clinical criteria.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

NEW: ANTI-ANGINAL AGENTS – MISCELLANEOUS

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<td>RANEXA® (ranolazine)</td>
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Clinical Criteria for Ranexa® (ranolazine):
Ranexa® (ranolazine) should be approved only for individuals with chronic angina who have failed to achieve an adequate response on at least two of the following agents:
- Beta-blocker
- Long-acting nitrate
- Calcium channel blocker (dihydropyridine only)

Ranexa® (ranolazine) should NOT be approved for individuals with any of the following contraindications:
- Pre-existing QT prolongation
- Hepatic function impairment (Child-Pugh classes A, B, or C)
- Receiving QT-prolonging drugs (including Class Ia and Class III antiarrhythmics, ziprasidone)
- On potent or moderately potent CYP3A inhibitors (including diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, ketoconazole and other azole antifungals)

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References
Ranexa™ (ranolazine extended-release tablets) prescribing information. CV Therapeutics, Inc. 2006.
NEW: ANTI-HYPERTENSIVES – PULMONARY ARTERIAL HYPERTENSION AGENTS

BACKGROUND

• There are three oral agents approved for the treatment of pulmonary arterial hypertension (PAH): Revatio® (sildenafil citrate), Tracleer® (bosentan), and Letairis (ambrisentan). In addition, there is an inhaled agent, Ventavis® (iloprost).
  
• Revatio® inhibits the phosphodiesterase type-5 (PDE5) enzyme in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. By inhibiting PDE5, Sildenafil increases cGMP within the pulmonary vascular smooth muscle cells, resulting in relaxation (vasodilation).

• Tracleer® and Letairis® are both endothelin receptor antagonists. Endothelin-1 (ET-1) is a neurohormone which binds to ET\textsubscript{A} and ET\textsubscript{B} receptors in the endothelium and vascular smooth muscle and causes vasoconstriction. ET-1 concentrations are elevated in the plasma and lung tissue of patients with PAH, suggesting a pathogenic role for ET-1 in this disease.

• Ventavis® is a synthetic analog of prostacyclin PGI\textsubscript{2}, which dilates systemic and pulmonary arterial vascular beds.

• Adverse events associated with the PAH agents are as follows:
  
  o Revatio® is commonly associated with headache, flushing, epistaxis, diarrhea, indigestion, dizziness, rash, and abnormal vision. In rare circumstances, use of Revatio® can result in myocardial infarction, non-arteritic ischemic optic neuropathy, and priapism.

  o Tracleer® and Letairis® are commonly associated with headache, edema, hypotension, palpitations, flushing, indigestion, decreased hemoglobin, and elevated liver enzymes. Less commonly, Tracleer® and Letairis® can cause hepatotoxicity and cirrhosis of the liver.

  o Ventavis® is associated with flushing, headache, increased cough, insomnia, nausea/vomiting, and syncope.

• A few trials have evaluated the impact of these agents on patients with PAH:
  
  o The Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) study was a 12-week trial which randomized 278 patients to placebo (n = 70) or sildenafil 3 times daily: 20 mg (n = 69), 40 mg (n = 68), or 80 mg (n = 71). The 80 mg tid dose was found to significantly improve 6-minute walk test results compared to placebo at weeks 4 and 12 (difference of 26 m compared to placebo at week 4 and 45 m compared to placebo at week 12). In addition, 35% of patients in the pooled sildenafil groups improved by 1 functional class compared with 7% of patients in the placebo group.

  o In the Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Hypertension (BREATHE-1), 213 patients with NYHA class III PAH were randomly assigned to receive placebo or 62.5 mg bosentan twice daily for 4 weeks followed by either of 2 doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks. At Week 16, patients treated with bosentan showed significant improvements in the 6-minute walking distance (difference of 44 m compared to placebo). The Borg dyspnea index and WHO functional class were also improved in the bosentan group.

  o Two 12-week randomized, double-blind, placebo-controlled studies (ARIES-1 and ARIES-2) examined the use of ambrisentan in 393 patients with PAH (predominantly WHO Class II and III) who were on current therapy with a combination of anticoagulants, diuretics, CCBs, or digoxin. ARIES-1 compared 5 mg and 10 mg of ambrisentan to placebo, while ARIES-2 compared 2.5 mg and 5 mg of ambrisentan to
cardiovascular agents

placebo. Both studies showed statistically significant improvements in 6-minute walk distance after 12 weeks of therapy with ambrisentan compared to placebo, and the improvements increased with dose. In ARIES-1, the mean change from baseline was 23 m with 5 mg ambrisentan, 44 m with 10 mg ambrisentan, and 8 m with placebo. In ARIES-2, the mean change from baseline was 22 m for 2.5 mg ambrisentan, 49 m with 5 mg ambrisentan, and 10 m with placebo.

- A random ambrisentan ized, double-blind, placebo-controlled trial examined the use of iloprost in 203 adult patients with NYHA Class III or IV PAH or pulmonary hypertension related to chronic thromboembolic disease who were receiving current therapy with anticoagulants, vasodilators, diuretics, oxygen, and digitalis. Patients received either iloprost 2.5 to 5 mcg or placebo given 6 to 9 times per day during waking hours. After 12 weeks, 19% more patients on iloprost showed a 10% improvement in exercise capacity (6-minute walk test) from baseline. The placebo-corrected difference 6-minute walk distance between iloprost and placebo was 40 m.

- The American College of Chest Physicians published updated guidelines for the treatment of PAH in June 2007. The updated guidelines recommend the following:
  - For Functional Class II patients: sildenafil (Level A evidence) or treprostinil (Level C evidence)
  - For Functional Class III patients, bosentan (Level A evidence), sildenafil (Level A evidence), IV epoprostenol (Level A evidence), iloprost (Level A evidence), or treprostinil (Level B evidence)
  - For Functional Class IV patients, IV epoprostenol (Level A evidence), bosentan (Level B evidence), iloprost (Level B evidence), sildenafil (Level C evidence), or treprostinil (Level C evidence)

**RECOMMENDATION**

Revatio®, Tracleer®, Letairis®, and Ventavis® all represent reasonable options for the treatment of PAH; however, their use may vary depending on the stage of PAH. The updated ACCP guidelines for PAH support Revatio® as first line therapy for WHO Functional Class II patients; whereas Revatio®, Tracleer®, and Ventavis® are recommended for WHO Functional Class III patients. In addition, Tracleer® and Ventavis® have stronger data to support their use in patients with more advanced disease (late WHO Functional Class III and Class IV). For patients failing to improve on single-agent therapy, combination therapy may be considered.

Given the impact of functional status on recommended treatments, as well as the different mechanisms of action and side effect profiles of available therapies, and the need for combination therapy in select patients, it is recommended that at least one phosphodiesterase-5 enzyme (PDE5) inhibitor agent, at least one endothelin receptor antagonist, and at least one prostacyclin analog be available for individuals with a diagnosis of PAH. However, due to the numerous, off-label uses of Revatio® and its potential to cause serious adverse events (myocardial infarction, non-arteritic ischemic optic neuropathy, priapism, etc.), it is recommended that Revatio® be subject to clinical criteria in order to ensure it is being used for PAH.

**COMMITTEE VOTE:**

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NEW: ANTI-HYPERTENSIVES – PULMONARY ARTERIAL HYPERTENSION AGENTS

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**Quantity Limits**

Revatio®: 3/day

**Clinical Criteria for Revatio® (sildenafil)**

Revatio® (sildenafil) will be approved only for the treatment of Pulmonary Arterial Hypertension (PAH) / Primary Pulmonary Hypertension (PPH).

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

**References**


NEW: VASOPRESSORS

BACKGROUND
- There is currently one oral vasopressor agent available—ProAmatine® (midodrine). This product is indicated for the treatment of orthostatic hypotension in patients whose lives are considerably impaired despite standard clinical care, fluid expansion, and lifestyle alterations.
- Midodrine forms an active metabolite, desglymidodrine, that serves as an alpha-1 agonist, producing an increase in vascular tone and blood pressure.
- Midodrine can cause marked elevations in both supine and sitting blood pressure. Midodrine should not be used in patients with pretreatment systolic BP > 180 mm Hg, as these patients are thought to be at an increased risk for supine hypertension.
- The most common side effects associated with midodrine are hypertension, piloerection, pruritus, shivering, paresthesia, and dysuria. In addition, midodrine has a 13.4% incidence of increased supine systolic arterial pressure of 200 mmHg or above.
- There are currently no large scale outcomes trials or national guidelines pertaining to midodrine use.

RECOMMENDATION
Midodrine can be a useful agent in the treatment of orthostatic hypotension in individuals who continue to be symptomatic (experiencing dizziness, syncope, etc.) despite standard clinical care, fluid expansion, and lifestyle alterations. While there is a significant risk of supine systolic hypertension, it is difficult to identify the recipients who are most at risk for this adverse event. Risk assessment is usually based on pre-treatment blood pressure readings, and this information is not always available in situations where patients switch physicians. Therefore, it is recommended that midodrine be available for individuals with symptomatic orthostatic hypotension.

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NEW: VASOPRESSORS

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NEW: CARDIAC GLYCOSIDES

BACKGROUND

- Cardiac glycosides are used for the treatment of mild to moderate heart failure and to control ventricular response rate in patients with chronic atrial fibrillation.
- Digoxin inhibits sodium-potassium ATPase, leading to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The increased calcium uptake by the cell improves the efficiency of excitation-contraction coupling of cardiac muscle, resulting in increased myocardial contractility. Digitalis also increases vagal stimulation, resulting in reduced sympathetic tone, decreased conduction velocity through the AV node, and decreased rate of impulse generation in the SA node.
- In general, the adverse reactions of cardiac glycosides are dose dependent and occur at doses higher than those needed to achieve a therapeutic effect. High doses of digoxin may produce a variety of rhythm disturbances, such as first, second, or third-degree heart block, AV dissociation, ventricular tachycardia, and ventricular fibrillation. Digoxin may also produce blurred or yellow vision and GI upset (nausea, vomiting, or diarrhea).
- There are several studies that have examined the impact of digoxin:
  - Two 12-week, double-blind, placebo-controlled studies investigated the benefits of digoxin in New York Heart Association (NYHA) class II or III heart failure patients. PROVED enrolled 88 patients treated with digoxin and a diuretic. RADIANCE enrolled 178 patients treated with digoxin, a diuretic, and an ACE inhibitor. Both trials randomized participants to either continue digoxin or receive placebo. The results for both studies demonstrated better preservation of exercise capacity in patients randomized to digoxin. Continued treatment with digoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy.
  - The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6,801 patients with heart failure and left ventricular ejection fraction less than or equal to 0.45. Patients were randomized to receive either digoxin or placebo (in addition to diuretics and ACE inhibitors). The results demonstrated no difference in mortality between the two treatment groups; however there was a trend towards decreased death due to worsening heart failure in the digoxin group. Also, digoxin use was associated with a 25% reduction in the number of hospitalizations for heart failure, 28% reduction in the risk of a patient having at least 1 hospitalization for heart failure, and 6.5% reduction in total hospitalizations (for any cause).
  - Based on the current clinical literature, the greatest benefit of digoxin is seen among patients at with ejection fractions of 25% or less, those with cardiomegaly, and those in New York Heart Association functional class III or IV. Other clinical trials suggest that characteristics such as a low cardiac index, a high pulmonary capillary wedge pressure, or the presence of a third heart sound (S3 gallop) are also strong predictors of digoxin benefit in patients with CHF in normal sinus rhythm. The beneficial hemodynamic effects of digoxin are additive to those of angiotensin-converting-enzyme inhibitors.
- The 2005 ACC/AHA Guidelines for CHF recommend digoxin (in addition to diuretics, ACE inhibitors/ARBs, and beta-blockers) for patients with current or prior symptoms of HF and reduced LVEF.
RECOMMENDATION

Digoxin represents a useful drug in the treatment of heart failure. Based on available studies, digoxin use has been associated with improved exercise capacity, reduced progression of heart failure, and reduced hospitalizations for CHF patients. For this reason, it is recommended that digoxin be available on the PDL.

COMMITTEE VOTE:

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NEW: CARDIAC GLYCOSIDES

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NEW: ANTI-ARRHYTHMICS, ORAL

BACKGROUND
- There are several different classes of oral anti-arrhythmic drugs:
  - Class I anti-arrhythmics inhibit the transmembrane influx of sodium
    - Class Ia (quinidine, procainamide, and disopyramide) is effective at treating both supraventricular and ventricular arrhythmias.
    - Class Ib (mexiletine) is more effective at treating ventricular arrhythmias than supraventricular arrhythmias.
    - Class Ic (flecainide, propafenone, moricizine) is mainly used for treating supraventricular arrhythmias.
  - Class II anti-arrhythmics are beta-adrenergic blockers, used mainly to treat SA and AV nodal arrhythmias (these products were reviewed previously in the packet).
  - Class III anti-arrhythmics prolong refractoriness in atrial and ventricular fibers by blocking potassium channels. Class III anti-arrhythmics are mainly used for supraventricular tachyarrhythmias. The oral Class III drug includes amiodarone and dofetilide.
  - Class IV anti-arrhythmics are calcium-channel blockers, used mainly to treat SA and AV nodal arrhythmias (these products were reviewed previously in the packet).
- The various classes of anti-arrhythmics differ in their actions on the heart and thus, the types of arrhythmias they are used to treat.
- All anti-arrhythmics are associated with adverse events. Some of the most common adverse events encountered with all of the anti-arrhythmics are hypotension, dizziness, syncope, nausea, and vomiting. Serious side effects associated with these products include cardiac dysrhythmia, chest pain, torsade de pointes, hepatotoxicity, hematologic disorders, and SLE.
- Current guidelines from the American College of Physicians and the American Academy of Family Physicians (2003) recommend the following drugs for patients whose lives are compromised by atrial fibrillation (and could benefit from rhythm maintenance): amiodarone, disopyramide, propafenone, and sotalol.
- The ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation support the use of pharmacologic agents for cardioversion to sinus rhythm in patients with persistent atrial fibrillation. In addition, they recommend the use of sotalol or amiodarone for patients at increased risk of developing post-operative atrial fibrillation.
- No guidelines are available for the treatment of ventricular arrhythmias.

RECOMMENDATION
Given the differences in mechanism of action and effect between the different anti-arrhythmics, these agents cannot be deemed therapeutic alternatives. Even within the sub-classes of anti-arrhythmics, there are distinct differences in effect and adverse event profiles. For this reason, it is recommended that the various unique chemical entities included in the Anti-Arrhythmic class all be made available.

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NEW: ANTI-ARRHYTHMICS, ORAL

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References


NEW: HEMOSTATICS, ORAL

BACKGROUND
- There is currently one oral hemostatic agent available—Amicar® (aminocaproic acid). This product is indicated for the treatment of hemorrhage (when fibrinolysis contributes to bleeding), as well as hematuria (both surgical and non-surgical).
- The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity.
- When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation (DIC), this distinction must be made before administering aminocaproic acid because aminocaproic acid administered to a patient with DIC may produce potentially fatal thrombus formation.
- The most common side effects associated with aminocaproic acid are nausea, vomiting, asthenia, dizziness, and headache. Its use has also been associated with bradyarrhythmia, hypotension, rash, thrombotic disorder, drug-induced myopathy, rhabdomyolysis, and renal failure.
- According to the 2006 Institute for Clinical Systems Improvement (ICSI) Anticoagulation Therapy Supplement, aminocaproic acid may be a useful treatment option for patients on anticoagulant therapy who are undergoing low bleeding-risk procedures, such as dental procedures, skin biopsies, and cataract surgery. Aminocaproic acid was presented, along with pressure, topical thrombin, and gelatin sponges, as a reasonable option to help control local bleeding, without having to alter the patient’s dose of warfarin.
RECOMMENDATION

As the only oral hemostatic agent, aminocaproic acid represents a useful drug for the treatment of individuals experiencing hemorrhage due to fibrinolysis, hematuria (both surgical and non-surgical), and undergoing low bleeding-risk procedures. For this reason, it is recommended that aminocaproic acid be available on the PDL.

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NEW: HEMOSTATICS, ORAL

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References


RE-REVIEW: PLATELET AGGREGATION INHIBITORS

BACKGROUND

- Inhibitory effects on the aggregation of platelets have lead to a significant decrease in the rate of vascular events for both primary and secondary cardiovascular prevention trials. They are useful in the treatment and prevention of cardiovascular and cerebrovascular thrombotic events.
- The platelet aggregation inhibitors discussed in this review are distinctively different in their mechanisms of action.
  - Aspirin is the oldest antiplatelet agent and works via irreversible inhibition of cyclooxygenase.
  - Dipyridamole (Persantine®) inhibits the uptake of adenosine into platelets, resulting in increased levels of platelet cyclic-3',5'-adenosine monophosphate (cAMP), and ultimately inhibition of platelet aggregation in response to stimuli such as platelet activating factor (PAF), collagen, and adenosine diphosphate (ADP).
  - Aggrenox®, the combination of aspirin and extended-release dipyridamole, utilizes the two different mechanisms of action of its components to inhibit platelet aggregation.
  - Clopidogrel and ticlopidine inhibit the binding of adenosine diphosphate (ADP) to their platelet receptors and subsequently inhibit platelet aggregation.
- Hematologic adverse reactions are the major concern for this group of drugs. Serious side effects associated with this class include thrombocytopenia and agranulocytosis, both of which occur more frequently with ticlopidine. A significant drug-drug interaction between clopidogrel and two widely used statins has recently been published; atorvastatin and simvastatin substantially decrease the antiplatelet activity of clopidogrel.
• There are several studies that have examined the antiplatelet agents:
  o The CAPRIE study is a large study (n=19,185) that looked at the use of clopidogrel (75 mg once daily) vs. aspirin (325 mg once daily) in patients with recent MI, stroke, or established peripheral arterial disease (PAD). This study found that clopidogrel use was associated with an overall risk reduction in the combined end points of first occurrence of MI, stroke, or other vascular death.
  o The CURE study was another large study (n=12,562) that evaluated the efficacy and safety of clopidogrel when administered with aspirin in patients with acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction). This study found that the combination of aspirin and clopidogrel produced a 20% relative risk reduction in the combined end points of MI, stroke, or cardiovascular death, with an absolute event rate of 9.3% in the clopidogrel group and 11.4% in the placebo group.
  o The European Stroke Prevention Study (ESPS) compared treatment with aspirin, dipyridamole ER, the combination of both, or placebo in patients with a history of stroke or TIA within 3 months of study entry. The results showed that stroke risk was significantly reduced by 18.1% in the aspirin-alone group, by 16.3% in the dipyridamole-alone group, and by 37.0% in the combination group compared to the placebo group.
  o The CLASSICS trial compared clopidogrel to ticlopidine in 1,020 patients who had undergone coronary stenting. This study found that ticlopidine had a higher incidence of neutropenia, thrombocytopenia and major bleeding than clopidogrel, although efficacy was comparable with regards to cardiovascular events.
• According to the most recent guidelines from both the American Heart Association and the American Academy of Neurology, the use of aspirin or clopidogrel is recommended as first line therapy for the majority of patients with vascular disease. The American College of Cardiology has recommended acute and long-term antiplatelet treatment with aspirin, clopidogrel, or the combination of the two agents for patients with acute coronary syndromes or myocardial infarction. In stroke prevention, the combination of aspirin and dipyridamole (Aggrenox®) as well as the ADP antagonists (clopidogrel and ticlopidine) have demonstrated favorable outcomes in clinical trials. However, dipyridamole monotherapy has not been proven efficacious in stroke prevention.

**RECOMMENDATION**

Platelet aggregation inhibitors are used to prevent and treat a variety of thrombotic events including MI, stroke and TIA, and peripheral artery disease. Clinical data suggests similar efficacy between aspirin, dipyridamole, ticlopidine, clopidogrel, and the aspirin/dipyridamole combination product in preventing recurrent vascular events among patients with vascular disease. According to the most recent guidelines from both the American Heart Association and the American Academy of Neurology, the use of aspirin or clopidogrel is recommended as first line therapy for the majority of patients with vascular disease. In addition, given the studies showing greater efficacy for the combination aspirin/dipyridamole ER product compared to its individual components, it is recommended that this combination be made available, as well.

**COMMITTEE VOTE:**

APPROVED    DISAPPROVED    APPROVED with MODIFICATION
RE-REVIEW: PLATELET AGGREGATION INHIBITORS

<table>
<thead>
<tr>
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<tr>
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<td>PERSANTINE® (dipyridamole)</td>
</tr>
<tr>
<td>DIPYRIDAMOLE (compare to Persantine®)</td>
<td>TICLID® (ticlopidine)</td>
</tr>
<tr>
<td>AGGRENOX® (dipyridamole extended release/aspirin)</td>
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</tr>
<tr>
<td>PLAVIX® (clopidogrel)</td>
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</tr>
<tr>
<td>TICLOPIDINE (compare to Ticlid®)</td>
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</tr>
</tbody>
</table>

References


Ticlid® Product Information, Roche Laboratories, November 2003.


NEW: INTERMITTENT CLAUDICATION

BACKGROUND

- Intermittent claudication due to lower extremity peripheral arterial diease (PAD) is characterized by temporary pain brought on by muscle exertion usually in the calf muscles. Agents in this class are used to reduce symptoms of intermittent claudication.
- The agents in this class have different mechanisms of action.
  - Cilostazol and its active metabolites inhibit phosphodiesterase activity and suppress degradation of cyclic adenosine monophosphate (cAMP) resulting in an increase in cAMP in platelets and blood vessels. It reversibly inhibits platelet aggregation induced by various stimuli, including thrombin, adenosine diphosphate (ADP), collagen, arachidonic acid, epinephrine, and shear stress. Cilostazol produces non-homogenous vasodilation, with greater dilation in femoral beds than in vertebral, carotic, or superior
mesenteric arteries, but without effect in renal arteries. Modest effects on circulating plasma lipids have been examined in patients taking cilostazol.

- Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity, thereby increasing blood flow to the affected microcirculation and enhancing tissue oxygenation.

- These agents are generally well tolerated. Common side effects seen with cilostazol include headache, diarrhea, and palpitations. Common adverse reactions with pentoxifylline include dyspepsia, dizziness, GI disturbances, and nausea. Cilostazol is contraindicated in patients with congestive heart failure of any severity due to the inhibition of phosphodiesterase. It is also contraindicated in patients with active bleeding such as bleeding peptic ulcers, intracranial disorders, and patients with hemostatic disorders. Pentoxifylline is contraindicated in patients with recent cerebral or retinal hemorrhage.

- There are several studies that have examined the intermittent claudication agents:
  - The ability of cilostazol to improve walking distance in patients with stable intermittent claudication was studied in 8 large, randomized, placebo-controlled, double-blind trials of 12- to 24-week duration using dosages of 50 mg twice daily (n = 303), 100 mg twice daily (n = 998), and placebo (n = 973). Efficacy was determined primarily by the change in maximal walking distance from baseline (compared with change on placebo) on one of several standardized exercise treadmill tests. Compared with patients treated with placebo, patients treated with cilostazol 50 or 100 mg twice daily experienced statistically significant improvements in walking distances both for the distance before the onset of claudication pain and the distance before exercise-limiting symptoms supervened (maximal walking distance). The effect of cilostazol on walking distance was seen as early as the first on-therapy observation point of 2 or 4 weeks.
  - One meta-analysis consisting of six randomized trials examined the effects of pentoxifylline in intermittent claudication. This analysis concluded that pentoxifylline had small effects on pain-free and total walking distance.

- Walking distance in intermittent claudication can be improved by both exercise rehabilitation and by pharmacological treatments. Cilostazol has been shown to increase walking distance in patients treated with intermittent claudication. In the 2005 AHA/ACC Practice Guidelines on the management of PAD, cilostazol is recommended for patients with lifestyle-limiting intermittent claudication (in the absence of heart failure). The guidelines state that pentoxifylline may be considered as second-line therapy to cilostazol, as its effectiveness is not well-established.

**RECOMMENDATION**

Current clinical data, as well as treatment guidelines, recommend cilostazol as the agent of choice for the treatment of intermittent claudication. Its effectiveness at increasing walking distance in patients with lower extremity PAD and intermittent claudication has been well-established. Therefore, cilostazol should be considered the superior agent within this category, with pentoxifylline regarded as an inferior agent due to lack of effectiveness data.

**COMMITTEE VOTE:**

APPROVED       DISAPPROVED       APPROVED with MODIFICATION
### NEW: INTERMITTENT CLAUDICATION

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<tr>
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<tr>
<td>CILOSTAZOL (compare to Pletal®)</td>
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<tr>
<td>PENTOXIFYLLINE (compare to Trental®)</td>
<td>TRENITAL® (pentoxifylline)</td>
</tr>
</tbody>
</table>

### References


- Pletal (Package Insert). Rockville, MD; Otsuka America Pharmaceutical, 2005.

NEW: THYROID HORMONES

BACKGROUND

- Hypothyroidism is a disorder in which the thyroid gland fails to secrete adequate amounts of thyroid hormone. The majority of cases are due to primary thyroid gland failure because of chronic autoimmune (Hashimoto’s) thyroiditis, radioactive iodine therapy, or surgery. The physiological actions of thyroid hormones are produced predominantly by T₃, the majority of which (approximately 80%) is derived from T₄ by deiodination in peripheral tissues.
- Thyroid hormones, T(3) and T(4), are thought to act by binding to thyroid receptor proteins attached to DNA, thus activating gene transcription and protein synthesis. The physiological activities of thyroid hormones are produced primarily by T(3), and approximately 80% of T(3) is derived from T4 by deiodination in peripheral tissues.
- All agents in the class carry the following black boxed warning, “Do not use thyroid hormones, either alone or with other therapeutic agents, for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.”
- FDA Approved Indications are as follows:

<table>
<thead>
<tr>
<th>FDA Approved Indication</th>
<th>Levothyroxine (T₄)</th>
<th>Liothyronine (T₃)</th>
<th>Liotrix (a 4 to 1 mixture of T₄ and T₃)</th>
<th>thyroid desiccated</th>
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</thead>
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<tr>
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<td>Congenital hypothyroidism</td>
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<td>Thyroid stimulating hormone suppression</td>
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<td>✓</td>
</tr>
<tr>
<td>Simple Goiter</td>
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</table>

- Common side effects are as follows:

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Levothyroxine (T₄)</th>
<th>Liothyronine (T₃)</th>
<th>Liotrix (a 4 to 1 mixture of T₄ and T₃)</th>
<th>thyroid desiccated</th>
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<tbody>
<tr>
<td>Myocardial Infarction</td>
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<td>Osteopenia</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Pseudotumor cerebri</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Seizure</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
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<tr>
<td>Sweating</td>
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<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>✓</td>
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</table>

- The American Association of Clinical Endocrinologists (AACE) advocates the use of levothyroxine for thyroid replacement. Further, it states that desiccated thyroid hormone, combinations of thyroid hormone, or triiodothyronine should not be used for general thyroid replacement therapy.
- The American Thyroid Association also advocates the use of levothyroxine for general thyroid replacement. However, they identify liothyronine can be useful as short term therapy prior to treatment of thyroid cancer with radioactive iodine since patients can be withdrawn from liothyronine for shorter periods of time. Chronic liothyronine usage is discouraged due to a
greater occurrence of iatrogenic hyperthyroidism. Biological and synthetic thyroid hormone preparations containing both T3 and T4 are not recommended due to a fluctuating and often elevated T3 concentration.

RECOMMENDATION
Hypothyroidism requires exogenous thyroid hormone replacement. All of the thyroid hormones have similar FDA-approved indications and safety profiles. Levothyroxine sodium is the treatment of choice for the management of hypothyroidism. Liothyronine may be useful prior to treatment of thyroid cancer with radioactive iodine, because patients can be withdrawn from liothyronine for shorter periods of time; however, chronic liothyronine therapy for hypothyroidism is not recommended since its use is associated with a greater degree of iatrogenic hyperthyroidism. Biological and synthetic thyroid hormone preparations containing both T4 and T3 are also not currently recommended for therapy since they produce fluctuating T3 concentrations. Therefore, at least one levothyroxine and one liothyronine product should be available for use in patients with hypothyroidism.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

<table>
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<th>NEW: THYROID HORMONES</th>
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<td>CYTOMEL® (liothyronine)</td>
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References
NEW: ANTI-THYROID HORMONES

BACKGROUND

- Hyperthyroidism encompasses a heterogeneous group of disorders such as Graves’ disease, all characterized by elevated levels of thyroid hormones in the blood.
- Anti-thyroid hormones are iodinated and degraded within the thyroid gland. The iodination and metabolism of these agents results in diversion of oxidized iodide away from thyroglobulin effectively ceasing thyroid hormone biosynthesis. Unlike propylthiouracil, methimazole lacks the ability to block the peripheral conversion of thyroxine (T4) to triiodothyronine (T3).
- Both agents in this class are FDA-approved for hyperthyroidism only.
- Common side effects are as follows:

<table>
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<tr>
<th>Side Effect</th>
<th>Methimazole</th>
<th>Propylthiouracil</th>
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<td>Rash</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>Leukopenia</td>
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</tr>
<tr>
<td>Fever</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Nephritis</td>
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</tr>
</tbody>
</table>

- The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association advocate the use of methimazole and propylthiouracil for the treatment of hyperthyroidism both alone and in conjunction with radioactive iodine or surgery.

RECOMMENDATION

The treatment of hyperthyroidism is directed toward lowering the serum concentrations of thyroid hormones to reestablish a euthyroid state. While both propylthiouracil and methimazole are effective in the treatment of hyperthyroidism with similar safety profiles, methimazole lacks the ability to block the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) which limits its usefulness in the treatment of thyroid storm. With this in mind, propylthiouracil can be considered a superior agent in this class; however, to ensure provider choice, at least 2 agents in this class should be available for use.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

NEW: ANTI-THYROID HORMONES

PREFERRED   NON-PREFERRED
METHIMAZOLE (compare to Tapazole®)  
PROPYLTHIOURACIL  
TAPAZOLE® (methimazole)

References

NEW: ORAL CONTRACEPTIVES

BACKGROUND

- Oral contraceptives are available as combination estrogen/progestin products, as well as progestin-only products. Combination estrogen/progestin contraceptives are available as monophasic, biphasic, or triphasic formulations, based on whether they contain 1, 2, or 3 different dose combinations of estrogen/progestin hormones in the active pills. Progestin-only contraceptives tend to be less effective than combination oral contraceptive pills; however, they have great utility in women who are breastfeeding and women who cannot take (or are intolerant to) estrogen-containing products.

- Combination OCs inhibit ovulation by suppressing the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in reduced secretion of the gonadotropins FSH, and LH from the pituitary. Additionally, they result in the formation of more viscous cervical mucus which inhibits sperm penetration and the delayed maturation of the endometrium which reduces the likelihood of implantation. Progestin-only oral contraceptives work by suppressing ovulation, thickening the cervical mucus to inhibit sperm penetration, lowering the midcycle LH and FSH peaks, slowing the movement of the ovum through the fallopian tubes, and altering the endometrium.

- Among the combination estrogen/progestin products, the most common adverse events include: breast tenderness, headache, nausea/vomiting, upper respiratory infection, menstrual cramps, changes in menstrual flow, and abdominal pain. The combination products can also be associated with several serious, but less common adverse events such as: arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, coronary thrombosis, gallbladder disease, hepatic adenomas or benign liver tumors, hypertension, mesenteric thrombosis MI, pulmonary embolism, thrombophlebitis, and venous thrombosis with or without embolism.

- Common adverse events associated with progestin-only contraceptives include: menstrual irregularities, frequent and irregular bleeding, headache, breast tenderness, nausea, and dizziness. Androgenic side effects such as acne, hirsutism, and weight gain can occur, although rare, with the progestin-only products.

- According to guidelines published in the Journal of Family Planning and Reproductive Health Care, the use of progestogen-only contraceptives in the first 6 weeks postpartum does not appear to have an adverse effect on breast milk volume and provides over 99% efficacy; therefore it is a good choice for women post-partum.

- Available guidelines regarding contraceptives do not recommend any particular oral contraceptive over another; however, guidelines from Brigham and Women’s Hospital recommend low-dose estrogen products (containing 20 to 35 mcg estrogen) over the higher dose preparations that contain 50 micrograms of an estrogen.
RECOMMENDATION

Both estrogen/progestin oral contraceptives and progestin-only oral contraceptives can be considered safe and effective methods of contraception. While progestin-only products tend to be less effective than combination contraceptives, they have utility in women who are breastfeeding and women who cannot take (or are intolerant to) estrogen-containing products. For this reason, it is recommended that both combination estrogen/progestin oral contraceptives and progestin-only oral contraceptives be available on the PDL.

Among the available estrogen/progestin contraceptives, all products can be considered therapeutic alternatives to one another; however, the low-estrogen contraceptives cause fewer side effects such as weight gain, bloating, nausea, and breast tenderness, and have been linked to lower risk of stroke, MI, and venous thromboembolism. For this reason, it is recommended that low-dose estrogen alternatives be included among the available estrogen/progestin combination products.

Among the progestin-only oral contraceptives, all available products can be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
## New: Oral Contraceptives

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<tr>
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<td>API®</td>
<td>NOR-Q-D®</td>
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<tr>
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<td>NORA-BE®</td>
</tr>
<tr>
<td>AVIANE®</td>
<td>NORINYL® 1+35</td>
</tr>
<tr>
<td>BREVICON®</td>
<td>NORINYL® 1+50</td>
</tr>
<tr>
<td>CAMILLE®</td>
<td>NORTREL® 0.5/35</td>
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<td>ENPRESSE®</td>
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<td>ERRIN®</td>
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### References
NEW: NON-ORAL CONTRACEPTIVES

BACKGROUND

- There are currently two non-oral contraceptives available: Nuvaring® (etongestrel / ethinyl estradiol vaginal ring) and Ortho Evra® (norelgestromin / ethinyl estradiol transdermal patch). Nuvaring® is worn continuously for 3 weeks, then removed for 1 week, after which time a new ring is inserted. Ortho Evra® is applied once-weekly for 3 weeks, followed by a patch-free week.
- The combination of estrogen and progestin hormones present in both Nuvaring® and Ortho Evra® inhibit ovulation by suppressing the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in reduced secretion of the gonadotropins FSH and LH from the pituitary. Other effects include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and in the endometrium (which reduce the likelihood of implantation).
- Both Nuvaring® and Ortho Evra® display similar efficacy to oral contraceptives when used correctly.
- The package insert for Ortho Evra® contains a bolded warning stating that individuals who use Ortho Evra® achieve average steady state concentrations of ethinyl estradiol that are approximately 60% higher than those achieved with oral contraceptive pills containing 35 mcg of estrogen. This may result in an increased risk of adverse events, including venous thromboembolism.
- Common adverse reactions associated with the contraceptive transdermal patch include: breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps, and abdominal pain. Common adverse reactions associated with the contraceptive vaginal ring include: vaginitis, headache, upper respiratory tract infection, leukorrhea, sinusitis, weight gain, and nausea.
- A few head-to-head clinical trials have compared Nuvaring® to combination oral estrogen/progestin contraceptives, and found them to offer comparable efficacy and tolerability.
  - A randomized open-label trial involving 983 women compared Nuvaring® to a combined oral contraceptive containing 30 mcg ethinyl estradiol and 3 mg drospirenone. Over the course of 13 cycles, similar efficacy, compliance, and tolerability were demonstrated between the contraceptive ring and the oral contraceptive pills.
  - Another randomized, open-label trial compared Nuvaring® to combined oral contraceptives containing 15 mcg ethinyl estradiol and 120 mg etonogestrel or 30 mcg ethinyl estradiol and 150 mg levonorgestrel among 1030 women. Data collected over a time frame of 13 cycles failed to show any significant differences between the contraceptives with regards to efficacy, compliance, or tolerability.
- A few head to head studies were identified comparing Ortho Evra® use to oral contraceptive use. These studies present mixed conclusions as to whether Ortho Evra® offers an advantage over oral contraceptive pills.
  - Two multicenter trials comparing compliance with the contraceptive patch versus oral contraceptives showed improved compliance with the patch. The first trial compared Ortho Evra to Mercilon (150 mcg desogestrel, 20 mcg ethinyl estradiol, available only in Europe) among 1,517 women. It demonstrated similar efficacy and tolerability rates between the two products, but better compliance with Ortho Evra (94.4% vs. 87.8%). The second trial compared Ortho Evra to Triphasil among 1,417 women and showed similar efficacy and tolerability between treatments, with higher rates of perfect
compliance among Ortho Evra users (88.2%) compared to Triphasil users (77.7%), p<0.001.

- Another study involved 1,230 contraceptive-naïve women and monitored discontinuation rates, adverse events, and pregnancy outcomes over one year. This study found lower continuation rates for the patch formulation than the oral contraceptive pills (continuation rates at one year were 76% for the pill formulation and 57% with the patch, p=0.004). In addition, the patch formulation was associated with higher unintended pregnancy rates (RR = 3.23, 95% CI 1.43-7.31, p=0.005).

- Treatment guidelines from Brigham and Women’s Hospital state that Ortho Evra® and Nuvaring® may improve compliance over oral contraceptive pills; however, they warn that Ortho Evra® may be less effective in obese women (>198 pounds).

**RECOMMENDATION**

Nuvaring® and Ortho Evra® represent treatment alternatives to oral contraceptives. In clinical trials, these non-oral contraceptives have demonstrated similar efficacy and tolerability to oral contraceptives. However, given the high cost associated with these agents, as well as the greater estrogen exposure and potential for increased risk of venous thromboembolism associated with Ortho Evra®, it is recommended that these agents be reserved for those individuals who try and fail or are intolerant to an oral contraceptive agent, have a history of non-compliance with oral contraceptives, or are thought to be at risk for non-compliance with an oral regimen.

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

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<td>NUVARING® (etonogestrel / ethinyl estradiol) vaginal ring CC</td>
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**Clinical Criteria for Ortho-Evra® and Nuvaring®:**

Ortho-Evra® and Nuvaring® will be approved for individuals meeting one of the following criteria:

- At risk for non-compliance with an oral contraceptive
- History of non-compliance with an oral contraceptive
- Trial and intolerance or failure with at least one oral contraceptive

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
NEW: INJECTABLE CONTRACEPTIVES

BACKGROUND

- Depo-Provera is the only injectable contraceptive currently allowed to be billed on the pharmacy side. (All other injectable contraceptives must be billed under the medical benefit). It is administered once every 3 months, either via an intramuscular or subcutaneous injection.
- Depo-Provera is used primarily for contraception, but can also be used for treatment of endometriosis or as adjunctive or palliative treatment for inoperable, recurrent, metastatic endometrial or renal carcinoma. Depot medroxyprogesterone acetate is approved for contraception at a dose of 104 mg SQ or 150 mg IM, and for endometriosis at a dose of 104 mg SQ every 3 months.
- When administered parenterally, medroxyprogesterone acetate exerts its physiological effects by transforming proliferative endometrium into secretory endometrium and by inhibiting gonadotropin production thereby preventing follicle maturation and ovulation.
- Studies of the effectiveness of depot medroxyprogesterone acetate as a contraceptive have shown it to be over 99% effective, when administered appropriately every 3 months.
- Common adverse reactions experienced with depot medroxyprogesterone acetate include abdominal pain, menstrual changes including amenorrhea or breakthrough bleeding, weight changes, dizziness, and headache.
  - In addition, medroxyprogesterone acetate carries the following black box warning, “Women who use medroxyprogesterone acetate injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of medroxyprogesterone acetate during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. Medroxyprogesterone acetate should be used as a long-term birth control method (eg, longer than 2 years) only if other birth control methods are inadequate.”
- Few head to head clinical trials have compared the efficacy and safety of depot medroxyprogesterone acetate to other contraceptives.
One observational prospective cohort study compared repeat pregnancy rates among 252 adolescents who chose Depo-Provera (n=142), Ortho-Evra (n=55), or oral contraceptive pills (n=55) for their postpartum contraception. After 1 year, the repeat pregnancy rates were 14.2% among Depo-Provera users, 29.7% among oral contraceptive pill users, and 31.8% among contraceptive patch users.

Other studies have compared the impact of Depo-Provera versus other contraceptives on bone mineral density rates. One study involving 31 adolescents on various hormonal contraceptives showed that patients receiving Depo-Provera experience a 3.1% reduction in bone mineral density after 2 years of use, whereas individuals on Norplant and oral contraceptives showed an increase in bone mineral density.

Place in Therapy:
- The American Academy of Pediatrics recommends the use of depot medroxyprogesterone acetate for adolescents who have chronic illness, are lactating, or are at risk for complications with estrogens. The Academy further advocates the use of depot medroxyprogesterone in patients who do not remember to take daily medications.
- The American College of Obstetricians and Gynecologists (ACOG) states the use of oral contraceptives and oral or depot medroxyprogesterone may be equivalent to other more costly regimens for the treatment of pain associated with endometriosis.

**RECOMMENDATION**
Depot medroxyprogesterone acetate is a useful agent for the prevention of pregnancy with similar safety and efficacy as other hormonal contraceptives. Depot medroxyprogesterone has also found utility in the treatment of pain induced by endometriosis; however, oral medroxyprogesterone should be utilized if possible. Due to its utility in the prevention of pregnancy, especially in patients who are non-compliant with daily oral medications, it is recommended that depot medroxyprogesterone acetate be made available.

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

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<tr>
<td>MEDROXYPROGESTERONE ACETATE 150 MG/ML</td>
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<td>DEPO SUBQ PROVERA® 104 MG/0.65 ML</td>
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**References**

RE-REVIEW: ORAL ESTROGENS

BACKGROUND

- There are several oral estrogens available. The different products contain varying types of estrogen; however, they all have been shown to be safe and effective in treating vasomotor symptoms of menopause. Although FDA-approved indications vary, it is thought that all products also offer similar benefits in relieving vaginal symptoms/atrophy associated with menopause, as well as prevention of post-menopausal osteoporosis.
- Around the time of menopause, estrogen levels drop, resulting in various symptoms including hot flashes, night sweats, and vaginal dryness. Estrogen replacement therapy increases estrogen levels, and reduces elevated levels of LH and FSH, thus helping to combat the symptoms of menopause.
- Common side effects associated with oral estrogens include headache, abdominal pain, N/V, weight changes, breast pain, dysmenorrhea/breakthrough bleeding, and vaginal candidiasis.
- Based on findings from the Women’s Health Initiative study, it is now known that estrogen agents can increase one’s risk of stroke, deep vein thrombosis, and pulmonary embolism. For this reason, it is recommended that oral estrogens be used at the lowest effective dose for the shortest amount of time for the relief of menopause symptoms.
- There are few head to head studies available comparing the different oral estrogen products. A meta-analysis of available trials concluded that all estrogen agents significantly reduced the weekly number of hot flashes compared with placebo, and differences between estrogen agents were not statistically significant.
- March 2007 guidelines from The North American Menopause Society recommend estrogen agents for the treatment of moderate to severe vasomotor symptoms, as well as vaginal symptoms, of menopause. However, in situations where vaginal symptoms are the only indication, a local (not systemic) estrogen product is recommended. The guidelines further state that lower doses of estrogens may be safer than higher doses.

RECOMMENDATION

The oral estrogen agents are effective at reducing vasomotor and vaginal symptoms of menopause. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another. In order to ensure adequate patient and prescriber choice, it is recommended that at least 3 different agents be available. Given that Premarin® has the most clinical data, it is recommended that this product be included among the available agents.

COMMITTEE VOTE:

APPROVED          DISAPPROVED          APPROVED with MODIFICATION
RE-REVIEW: ORAL ESTROGENS

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References

RE-REVIEW: TRANSDERMAL ESTROGENS

BACKGROUND
- There are currently several different kinds of transdermal estrogen products available, including estradiol patches, estradiol gels, and an estradiol emulsion. All agents (with the exception of Menostar®) are approved for the relief of vasomotor symptoms of menopause. In addition, most other products are indicated for treatment of vaginal symptoms of menopause, as well as prevention of post-menopausal osteoporosis.
- Common adverse events associated with the estrogen products include: application site reactions, abdominal pain, headache, N/V, weight gain, breast pain, and dysmenorrhea/breakthrough bleeding.
- As with the oral estrogen products, the transdermal estrogens should be used at the lowest possible dose for the shortest amount of time needed, as these agents may increase one’s risk of stroke, deep vein thrombosis, and pulmonary embolism. However, some studies suggest that transdermal estrogens may pose a lower risk of DVT than oral estrogens.
- There have been several head to head studies evaluating the safety and efficacy of various transdermal estrogen formulations. In general, no significant differences in reduction of vasomotor symptoms have been identified among the various products; however, it appears that the matrix-type patches (e.g., Vivelle, Esclim) are associated with fewer application site reactions and better adhesion than the reservoir-type patch (e.g., Estraderm).
- According to the March 2007 guidelines from The North American Menopause Society, transdermal estrogen products are recommended as an alternative to oral estrogen agents for the treatment of moderate to severe vasomotor symptoms, as well as vaginal symptoms, of
menopause. However, as with the oral agents, in situations where vaginal symptoms are the only indication, a local (not systemic) estrogen product is recommended. Furthermore, the guidelines state that there is some evidence that the transdermal products may be associated with lower rates of VTE than the oral estrogen products; however the incidence of breast cancer appears to be similar between the oral and transdermal formulations.

RECOMMENDATION

The transdermal estrogens are effective at reducing vasomotor and vaginal symptoms of menopause. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another. Head to head trials suggest that the matrix patches are associated with fewer application site reactions and provide better adhesion than the reservoir patches. In order to ensure adequate patient and prescriber choice, it is recommended that at least 3 different transdermal estrogen products be available, of which at least one must be a matrix patch.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

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References

RE-REVIEW: VAGINAL ESTROGENS

BACKGROUND

- There are currently several different kinds of vaginal estrogen products available, including conjugated estrogen creams, estradiol creams, estropipate creams, estradiol vaginal tablets, and estradiol vaginal rings. All agents are approved for the relief of vaginal symptoms associated with menopause. Femring is also approved for treatment of menopausal vasomotor symptoms.
- Common adverse events reported with the vaginal estrogen products include: abdominal pain, headache, N/V, pruritus, weight gain, breast pain, dysmenorrhea/breakthrough bleeding, vaginitis, and vaginal candidiasis.
As with the oral estrogen products, the vaginal estrogens should be used at the lowest dose that controls symptoms for the shortest amount of time needed.

Three head to head studies have evaluating the safety and efficacy of various vaginal estrogen formulations.

- One study compared the conjugated estrogen cream to the estradiol vaginal tablet and found no difference in efficacy between the two products.
- Two studies compared the conjugated estrogen cream to the estradiol vaginal ring and found no difference in efficacy between the two products.

According to the March 2007 guidelines from The North American Menopause Society, vaginal estrogen products are recommended (over oral or transdermal agents) for the treatment of vaginal symptoms of menopause when hormones therapy is considered solely for this indication.

**RECOMMENDATION**

The vaginal estrogen products are effective at reducing vaginal symptoms of menopause. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another. In order to ensure adequate patient and prescriber choice, it is recommended that at least 2 different agents be available, of which at least one must be a cream formulation.

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

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**References**

RE-REVIEW: ORAL ESTROGEN/PROGESTIN COMBINATIONS

BACKGROUND
- There are several oral estrogen/progestin combination products currently available. These agents are used for the treatment of moderate to severe vasomotor symptoms of menopause, as well as for the treatment of vaginal symptoms and post-menopausal osteoporosis, in women with an intact uterus.
- While the estrogen component helps to counteract the drop in estrogen accompanying menopause (thus combating menopausal symptoms), the progestin component helps to suppress epithelial DNA synthesis in the endometrial tissue, thereby helping to prevent endometrial hyperplasia.
- Common adverse events seen with the combination estrogen/progestin products include: abdominal pain, headache, breast pain, N/V, depression, and dysmenorrhea/breakthrough bleeding.
- Head to head trials comparing the various oral estrogen/progestin combination products indicate that the use of the product containing ethinyl estradiol/norethindrone acetate is associated with fewer episodes of bleeding and/or spotting than the conjugated estrogen/medroxyprogesterone cream.

RECOMMENDATION
The oral estrogen/progestin agents are effective at reducing both the vasomotor and vaginal symptoms of menopause. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another. The majority of our current market share is in the conjugated estrogen/medroxyprogesterone product; however, head to head trials suggest that ethinyl estradiol/norethindrone acetate may provide better control of bleeding episodes and/or spotting than conjugated estrogens/medroxyprogesterone. For this reason, it is recommended that at least these two agents be available on the PDL.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: ORAL ESTROGENS

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References
RE-REVIEW: TRANSDERMAL ESTROGEN/PROGESTIN COMBINATIONS

BACKGROUND

- There are two transdermal estrogen/progestin combination products currently available: Combipatch® and ClimaraPro®. These agents are used for the treatment of moderate to severe vasomotor symptoms of menopause, as well as for the treatment of vaginal symptoms and post-menopausal osteoporosis, in women with an intact uterus.
- While the estrogen component helps to counteract the drop in estrogen accompanying menopause (thus combating menopausal symptoms), the progestin component helps to suppress epithelial DNA synthesis in the endometrial tissue, thereby helping to prevent endometrial hyperplasia and cancer.
- Common adverse events seen with the combination estrogen/progestin products include: application site reactions, abdominal pain, headache, breast pain, N/V, depression, and dysmenorrhea/breakthrough bleeding.
- No head to head trials comparing the two transdermal estrogen/progestin combination products have been performed.

RECOMMENDATION

The combination estrogen/progestin transdermal agents are effective at reducing both the vasomotor and vaginal symptoms of menopause. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

RE-REVIEW: ORAL ESTROGENS

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<td>COMBIPATCH® (estradiol/norethindrone acetate)</td>
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References

RE-REVIEW: ORAL PROGESTIN AGENTS

BACKGROUND

- The oral progestin products are indicated for the treatment of secondary amenorrhea or abnormal uterine bleeding, as well as for endometriosis.
- Progestins decrease pituitary secretion of LH and FSH through a negative feedback mechanism, thus preventing follicular maturation and ovulation. In addition, progestins counteract the proliferative effect of estrogen on the endometrium.
- Common adverse reactions reported with use of progestins include: breast pain/enlargement, nausea, depression, breakthrough bleeding, and weight changes.
- No head to head studies have been performed on the individual oral progestins; however, studies comparing combination estrogen/progestin agents showed a lower risk of bleeding episodes and/or spotting with ethinyl estradiol/norethindrone acetate compared to conjugated estrogens/medroxyprogesterone acetate.

RECOMMENDATION

The oral progestin agents have all been shown to be effective in the treatment of secondary amenorrhea or abnormal uterine bleeding and in the treatment of endometriosis. All agents in this class exhibit similar efficacy and safety, and can thus be considered therapeutic alternatives to one another. However, based on the results from clinical trials involving combination estrogen/progestin agents, norethindrone appears to cause fewer episodes of vaginal bleeding than medoxyprogesterone. For this reason it is recommended that norethindrone be available on the PDL. In order to ensure adequate patient and prescriber choice, it is recommended that at least 2 different oral progestins be available.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: ORAL PROGESTINS

PREFERRED

| MEDROXYPROGESTERONE ACETATE (compares to Provera®) |
| NORETHINDRONE ACETATE (compares to Aygestin®) |
| PROMETRIUM® (progesterone, micronized) |

NON-PREFERRED

| AYGESTIN® (norethindrone acetate) |
| PROVERA® (medroxyprogesterone acetate) |

References


NEW: ORAL GLUCOCORTICOIDs
BACKGROUND

- Oral glucocorticoids have been around for decades and have found utility in many disease states from general allergic reactions to specific cancers.
- The mechanisms by which glucocorticoids exert their actions are numerous.
  - Glucocorticoids decrease inflammation by stabilizing the lysosomes in neutrophils. This results in the prevention of degranulation and subsequent inflammation.
  - They also inhibit phospholipase A2 causing inhibition of the synthesis of prostaglandins and lipoxygenase.
  - Glucocorticoids cause up-regulation of anti-inflammatory genes by binding to glucocorticoid receptors and decreasing the stability of selected messenger RNA molecules which alter gene transcription.
  - Lastly, glucocorticoids inhibit cell migration in the area of injury, reverse the dilation in the area of injury, and increase vessel permeability resulting in decreased access of cells to the sites of injury.
- The oral glucocorticoids are FDA-approved for a variety of indications. The following list contains some common uses of oral glucocorticoids:
  - Treatment of allergic reactions
  - Exacerbations of autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis
  - Symptomatic relief of respiratory disorders, including asthma, fulminating or disseminated pulmonary tuberculosis, and aspiration pneumonitis
  - Treatment of select endocrine disorders, including adrenal cortical insufficiency and congenital adrenal hyperplasia
  - Treatment of dermatologic disorders, including severe psoriasis, Stevens-Johnson syndrome, and atopic dermatitis
  - Treatment of hematologic disorders including idiopathic thrombocytopenic purpura and acquired (autoimmune) hemolytic anemia
  - Treatment and palliative management of leukemias and lymphomas
  - Treatment of ophthalmic disorders, such as optic neuritis and diffuse posterior uveitis
- Common side effects associated with glucocorticoids include:
  - Sodium and fluid retention
  - Hypokalemia
  - Weight gain
  - Impaired wound healing
  - Thinning of the skin
  - Acne
  - Hyperglycemia
  - Hypertension
  - Loss of muscle mass
- With prolonged use of glucocorticoids, individuals can develop a Cushingoid state (e.g., moonface, buffalo hump, central obesity), osteoporosis, and glucose intolerance. Children can also experience growth suppression.
- While the available glucocorticoids differ in their FDA-approved indications, practice guidelines often do not distinguish between the various glucocorticoids, or recommend an established agent that may not have the specific indication.
  - Betamethasone is the only oral glucocorticoid which carries a FDA indication for gout, systemic lupus erythematosus, and sarcoidosis; however, many treatment algorithms advocate the use of any glucocorticoid, or specifically prednisone, for these indications. In addition, betamethasone is also the only agent in this category with an
indication for temporal arteritis; however, treatment guidelines suggest the use of prednisolone.

- Budesonide is the only oral glucocorticoid which carries a FDA indication for rhinitis; however rhinitis is usually treated by the intranasal route. When treated systemically, guidelines recommend an oral glucocorticoid, without specifying a particular agent.
- Dexamethasone is recommended for prophylaxis and treatment of chemotherapy-induced nausea and vomiting. In addition, dexamethasone is useful in preventing postoperative and radiation-induced nausea and vomiting.
- Prednisone and prednisolone are generally considered the glucocorticoids of choice for anti-inflammatory or immunosuppressant effects.

- Of note, the American Gastroenterological Association guidelines on the treatment of inflammatory bowel disease recommend ileal-release preparations of budesonide as first line therapy for patients with mild to moderate Crohn’s disease, including ileal and right-sided Crohn’s disease and distal inflammation of the colon. Conventional corticosteroids, such as prednisone, are reserved for patients who fail to respond to budesonide.

RECOMMENDATION

The oral glucocorticoids work in many ways to decrease inflammation, regulate the body’s immune response, and control metabolism of protein and fat. For these reasons, these agents have utility in many disease states. While the FDA-approved indications may differ among the agents, many treatment guidelines do not specify an agent of choice. The side effect profiles of oral glucocorticoids vary as well. Therefore, it is recommended that all generic glucocorticoids be made available in order to ensure a wide range of therapeutic options and a variety of different side effect profiles. In addition, due to the role of ileal-release budesonide as first-line treatment in mild to moderate Crohn’s disease, it is recommended that this agent be made available for patients with this diagnosis.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

NEW: ORAL GLUCOCORTICOIDS

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Clinical Criteria for Entocort EC®

- Entocort EC will be approved for individuals with a diagnosis of mild to moderate Crohn’s disease involving the ileum or the ascending colon.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
NEW: ORAL MINERALOCORTICOIDS

BACKGROUND

- Mineralocorticoids act on the renal distal tubules to enhance the reabsorption of sodium and increase urinary excretion of potassium and hydrogen ions. Because of these effects on electrolyte levels, fludrocortisone, in small oral doses, causes a rise in blood pressure. In larger oral doses, fludrocortisone inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion. Fludrocortisone also promotes the deposition of liver glycogen, and unless protein intake is adequate, induces negative nitrogen balance.

- Fludrocortisone is FDA approved for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison disease and for the treatment of salt-losing adrenogenital syndrome in adults.

- Common side effects are as follows: edema, bruising, impaired wound healing, petechiae, rash, urticaria, decreased body growth, electrolyte imbalances, abdominal distension, peptic ulcer disease, myopathy, muscle weakness, headache, vertigo, glycosuria, and irregular periods. Sever adverse effects of fludrocortisones include: cardiomegaly, congestive heart failure, hypertension, thrombophlebitis, hypocortisolism, raised intracranial pressure, and seizure.

- Place in therapy:
  - Fludrocortisone is an adjunct to glucocorticoids in the management of primary adrenocortical insufficiency and salt-losing adrenogenital syndrome.
  - Although not FDA approved, fludrocortisone is the cornerstone of therapy for idiopathic orthostatic hypotension.
ENDOCRINE AGENTS

RECOMMENDATION
Mineralocorticoids work to enhance sodium levels and excrete potassium. Fludrocortisone is the only oral mineralocorticoid available for the treatment of Addison’s disease and adrenocortical syndrome. Fludrocortisone has also found utility in the treatment of idiopathic orthostatic hypotension; therefore fludrocortisone should be made available.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

NEW: ORAL MINERALOCORTICOIDS

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References

NEW: ADRENOCORTICOTROPIC HORMONES

BACKGROUND
- Corticotropin, the only outpatient administered drug in this class, exerts its physiological effects by combining with a specific receptor on the adrenal cell plasma membrane stimulating the initial reaction involved in the synthesis of adrenal steroids by increasing the quantity of cholesterol within the mitochondria.
- Corticotropin is FDA-approved for a variety of indications similar to the glucocorticoids.
  - Treatment of allergic reactions
  - Exacerbations of multiple sclerosis
  - Treatment of disorders of the endocrine system, eye, GI tract, hematopoietic structure, respiratory system, and skin such as collagen disease
  - Neoplastic disease
  - Nephrotic syndrome
- Common/severe adverse drug effects are as follows: edema, congestive heart failure, cardiomegaly, hypertension, hyperglycemia, peptic ulcer disease, muscle weakness, psychosis pancreatitis, glaucoma and decreased growth in children.
- Place in Therapy:
  - Corticotropin is primarily used as a diagnostic aid for detecting adrenocortical insufficiency; however, corticotropin can be used to treat any medical condition that is responsive to corticosteroids.
  - Corticotropin is not superior to corticosteroids for any indication, because the response to corticotropin is less predictable than that of glucocorticoids.
- The product information for H.P. Acthar® states, “H.P. Acthar Gel has limited therapeutic value in those conditions responsive to corticosteroid therapy; in such cases, corticosteroid therapy is considered to be the treatment of choice.”
RECOMMENDATION
In general, corticotropin is of limited therapeutic value since the drug cannot be administered orally, its effectiveness is dependent on adrenocortical responsiveness, and the response to corticotropin is less predictable than that of glucocorticoids. Therefore, corticotropin should be reserved for those patients who are unable to absorb medications by mouth, or those patients who have a contraindication or intolerance to oral glucocorticoids.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

NEW: ADRENOCORTICOTROPIC HORMONES

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Quantity Limits
Injection Gel/Jelly: 80 U/ML  1/day
Injection Powder for Solution:  40 U 1/day

Clinical Criteria for Corticotropin
Corticotropin will be approved only for recipients who are self administering and meet one of the following criteria:
- Difficulty swallowing or inability to absorb PO medications; OR
- Contraindication or intolerance of oral glucocorticoids.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

References
NEW: AGENTS FOR GOUT

BACKGROUND

- Gout is a disease that results from the deposition of monosodium urate crystals in tissues of the body causing recurring attacks of joint inflammation. Chronic gout can lead to deposits of uric acid in and around the joints, decreased kidney function, and kidney stones.
- The mechanisms by which medications used for gout exert their physiologic actions are centered on decreased production, decreased deposition, or increased excretion of uric acid.
  - Allopurinol specifically decreases the production of uric acid by inhibiting the action of xanthine oxidase, the enzyme that converts hypoxanthine to uric acid. Allopurinol also increases reutilization of hypoxanthine and xanthine for nucleotide and nucleic acid synthesis. Allopurinol thereby decreases uric acid concentration in both serum and urine.
  - Colchicine interrupts urate crystal deposition in joint tissues and the resultant inflammatory response that initiates and sustains an acute attack. Colchicine also decreases leukocyte chemotaxis and phagocytosis and inhibits the formation and release of a chemotactic glycoprotein that is produced during phagocytosis of urate crystals.
  - Probenecid competitively inhibits the active reabsorption of urate at the proximal renal tubule thereby increasing the urinary excretion of uric acid and lowering serum urate concentrations.
  - Sulfinpyrazone increases urinary excretion of uric acid. Sulfinpyrazone also has antiplatelet activities.
- FDA-approved indications are as follows:
  - All agents in the class are indicated for prophylaxis against gouty attacks, but only allopurinol and colchicine are indicated for treatment of gouty attacks.
  - In addition, allopurinol is indicated for recurrent renal calculi and hyperuricemia secondary to cancer or tumor lysis syndrome.
  - Probenecid is also used as an adjunct to antibiotic therapy, especially in the treatment of gonorrhea in conjunction with penicillin or ampicillin.
- The side effect profiles vary among the different agents. Common side effects for each agent are listed below:
  - For allopurinol: rash/pruritis, nausea/vomiting/diarrhea, anemia/blood dyscrasias, myelosuppression, hepatotoxicity
  - For colchicine: nausea/vomiting/diarrhea, renal failure, myelosuppression, neuromyopathy
  - For probenecid: rash/pruritis, nausea/vomiting/diarrhea, loss of appetite, headache, anemia/blood dyscrasias, hepatotoxicity, nephrotic syndrome, acute gout
  - For probenecid/colchicine: rash/pruritis, nausea/vomiting/diarrhea, loss of appetite, headache, anemia/blood dyscrasias, myelosuppression, hepatotoxicity, neuromyopathy, nephrotic syndrome, acute gout
  - For sulfinpyrazone: rash/pruritis, nausea/vomiting/diarrhea, anemia/blood dyscrasias
- Dosage in key populations:
  - Allopurinol, colchicine and probenecid must be adjusted in patient with renal impairment.
  - Sulfinpyrazone must be used with caution in patients who are anticoagulated, have bleeding disorders, or have peptic ulcer disease.
ENDOCRINE AGENTS

- Place in Therapy:
  - Allopurinol is useful in the treatment of chronic gout, and chronic gout complicated by renal insufficiency or uric acid renal calculi. Allopurinol is preferred over uricosuric agents in hyperuricemic patients who excrete more than 1 g uric acid per 24 hours, which is often observed in leukemia, lymphoma, polycythemia vera, myeloid metaplasia, and malignancies in patients receiving cancer chemotherapy. Allopurinol is also used in the Lesch-Nyhan syndrome in children, effectively controlling serum uric acid levels and preventing nephropathy and tophi, but having minimal effect on neurologic abnormalities.
  - Colchicine is the agent of first choice to abort acute attacks of gout, particularly in patients intolerant of or unresponsive to nonsteroidal antiinflammatory drugs. Colchicine may be used prophylactically to reduce frequency of gout attacks, during the few days before and after elective surgery, or during the first several months after patients begin treatment with uricosurics or allopurinol to preclude acute gout attacks.
  - Probenecid is useful primarily for prophylaxis in patients with normal renal function and a 24 hour urinary excretion pattern of less than 1 g uric acid.
  - Although serum uric acid levels are significantly decreased with sulfinpyrazone, this may not reduce the frequency of acute gouty attacks.

- Comparative Studies:
  - Comparative studies evaluating the effectiveness of allopurinol and probenecid indicate that both drugs produce satisfactory reductions in serum uric acid in gout patients or hyperuricemia due to other causes.
  - Investigators reported in a comparative study of 58 gouty arthritis patients that there appeared to be no significant differences between probenecid and sulfinpyrazone with regard to reduction of joint pain and stiffness and decreases in urate tophi.

RECOMMENDATION
Agents for gout have different mechanisms to decrease uric acid thereby curing and preventing gout. Colchicine is the agent of choice for treatment of acute gouty attacks. Neither allopurinol nor probenecid is effective in the treatment of acute gouty attacks. In fact, both of these agents may precipitate an acute attack of gouty arthritis during initial therapy (first few months) and colchicine should be administered concurrently. Allopurinol is the drug of choice in patients with mild renal impairment. Probenecid has utility as an adjunct to antibiotic therapy especially in gonococcal infections. It is recommended that colchicine, allopurinol and probenecid be available for use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>NEW: AGENTS FOR GOUT</th>
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<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>ALLOPURINOL (compares to Zyloprim®)</td>
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<tr>
<td>COLCHICINE (compares to Colsalide®)</td>
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<tr>
<td>PROBENECID (compares to Benemid® and Probalan®)</td>
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<td>PROBENECID/COLCHICINE</td>
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NEW: BISPHOSPHONATES AND OTHER BONE RESORPTION SUPPRESSION AGENTS

BACKGROUND

- Various agents are available to increase bone mass for individuals at risk for, or with a diagnosis of, osteoporosis. The available agents fall into four main categories: bisphosphonates, calcitonins, selective estrogen receptor modulators (SERMs), and parathyroid hormone (PTH).

- Each category of bone agent has a unique mechanism of action.
  - The bisphosphonates adsorb to bone apatite and become incorporated into the bone. Osteoclasts are unable to adhere to bone surfaces containing bisphosphonates, and thus, osteoclast activity is inhibited and bone turnover reduced.
  - Calcitonins stimulate receptors on osteoclasts, resulting in a decrease in osteoclast activity.
  - SERMs bind to estrogen receptors, activating certain estrogenic pathways, resulting in decreased resorption of bone.
  - PTH is the primary regulator of calcium and phosphate metabolism in the bone and kidney. It reduces osteoblast apoptosis and increases osteoblast activity, as well as increases renal reabsorption of calcium and phosphate.

- The available bone agents vary in their FDA-approved indications. These indications are represented in the table below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment of osteoporosis</th>
<th>Prevention of osteoporosis</th>
<th>Treatment of glucocorticoid-induced osteoporosis</th>
<th>Treatment of Paget’s Disease</th>
<th>Treatment of heterotopic ossification</th>
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<tbody>
<tr>
<td>Alendronate (Fosamax®)</td>
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<td>Alendronate/Vitamin D (Fosamax Plus D®)</td>
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<td>Risendronate (Actonel®)</td>
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<td>Risendronate/Calcium (Actonel with Calcium®)</td>
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<td>Etidronate (Didronel®)</td>
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<td>Ibandronate (Boniva®)</td>
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<tr>
<td>Calcitonin-salmon (Miacalcin®, Fortical®)</td>
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<tr>
<td>Raloxifene (Evista®)</td>
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<tr>
<td>Teriparatide (Forteo®)</td>
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* Indication for post-menopausal women only.
Adverse events associated with the various bone agents are as follows:

- **Bisphosphonates**: Commonly associated with abdominal pain, constipation, diarrhea, flatulence, musculoskeletal pain, headache, and vomiting. Less common, serious adverse events include duodenal ulcer, esophageal erosions, esophageal perforation, esophageal stricture, esophagitis, gastric ulcer, ulcerative pharyngitis, esophageal ulceration.

- **Calcitonins**: Commonly associated with flushing (face or hands), injection site inflammation, nausea, vomiting, backache, and rhinitis. In rare circumstances has been linked to myocardial infarction, thrombophlebitis, anemia, anaphylaxis, epistaxis, cerebrovascular accident, and bronchospasm.

- **SERMs**: Commonly associated with hot flashes/sweats and leg cramps. In rare circumstances, can cause venous thromboembolism, cerebrovascular accident, and pulmonary embolism.

- **PTH**: Commonly associated with hypotension, syncope, rash, sweating, hyperuricemia, constipation, diarrhea, indigestion, nausea, vomiting, arthralgia, leg cramps, asthenia, dizziness, increased cough, pharyngitis, and rhinitis. Less commonly, use can be associated with angina.

There are several head-to-head outcomes trials comparing the various bone agents:

- **The FACT trial** was a randomized, double-blind trial that compared alendronate 70 mg once weekly to risendronate 35 mg once weekly among 1,053 patients over 12-months. Greater increases in bone mineral density (BMD) were seen in the alendronate group at all sites measured at 12 months (p<0.001) as well as 6-months (p<0.001). No significant differences in adverse events were noted between the two treatment groups. In an extension of this study carried out to 2 years of treatment, the alendronate group continued to exhibit greater increases in BMD from baseline than the risendronate group (p<0.001).

- **The REAL study** was a retrospective, observational study that compared the incidence of hip and non-vertebral fractures among women receiving risendronate 35 mg weekly vs. alendronate 35 or 70 mg weekly. After 6 months and 12 months of therapy, the risendronate group showed fewer hip and non-vertebral fractures than the alendronate group (p=0.05 for 12-month non-vertebral, 6-month hip, and 12-month hip fracture data).

- **Two randomized, double-blind, placebo-controlled comparative trials** examined the efficacy and tolerability of alendronate vs. raloxifene among post-menopausal women (n=487 and n=456) over 12 months. Both studies showed that alendronate use was associated with significantly greater increases in BMD at lumbar spine and hip sites compared to raloxifene (p<0.001). Furthermore, the reported incidence of GI events was similar between the two groups in both studies.

- **Two randomized, double-blind studies** compared alendronate to teriparatide in women with osteoporosis (n=146 and n=203) over 14-months and 18-months, respectively. Both studies showed superior increases in BMD with teriparatide compared to alendronate.

The American Association of Clinical Endocrinologists 2003 Guidelines for Prevention and Treatment of Post-Menopausal Osteoporosis recommend alendronate, risendronate, and raloxifene as reasonable options for prevention and treatment of osteoporosis based on Level 1 evidence. Teriparatide is also recommended for treatment (Level 1 evidence). Calcitonin is mentioned as a reasonable treatment option, as well, but its data is limited to modest BMD increases at spinal sites only (Level 2 evidence). The guidelines further recommend that a bisphosphonate (specifically, alendronate or risendronate) be used in all adult women who require 7.5 mg of prednisone or its equivalent for more than 3 weeks.
The 2005 National Institute for Clinical Excellence (NICE) guidelines for prevention of osteoporosis recommend a bisphosphonate (alendronate, risendronate, or etidronate) as first line therapy. Raloxifene is recommended for use in women who cannot take a bisphosphonate due to contraindication, intolerance, history of unsatisfactory response, or physical inability to comply with the special recommendations for bisphosphonate use. Teriparatide is recommended for women aged 65 and older who have had an unsatisfactory response or intolerance to bisphosphonates, and who have an extremely low BMD (T-score -4SD or below) or a very low BMD (T-score -3SD or below) plus multiple fractures.

RECOMMENDATION
The available bone resorption suppression agents all represent reasonable treatment options to increase BMD and decrease the incidence of fractures. Based on current treatment guidelines, bisphosphonates are considered the agents of choice for first line prevention and treatment of osteoporosis. Among the bisphosphonates, all agents produce similar improvements in BMD with similar tolerability, however, at present clinical data suggest that alendronate may produce greater increases in BMD compared to the other bisphosphonates. Raloxifene presents an alternative therapy to the bisphosphonates, as do the calcitonin products. The two available calcitonin products display similar efficacy and safety, and thus can be considered therapeutic alternatives to one another. These agents have additional utility in patients for whom oral therapy is not an option.

In order to meet patient and prescriber needs, it is recommended that at least one bisphosphonate, one SERM, and one calcitonin product be available.

Teriparatide is the most effective agent in this class at increasing BMD; however, due to its high cost and safety concerns, it is recommended that this agent be subject to clinical criteria.

COMMITTEE VOTE:

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**RE-REVIEW: BISPHOSPHONATES AND OTHER BONE RESORPTION SUPPRESSION AGENTS**

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<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
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<tbody>
<tr>
<td>EVISTA® (raloxifene)</td>
<td>ACTONEL® (risendronate)</td>
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<tr>
<td>FOSAMAX® (alendronate)</td>
<td>ACTONEL WITH CALCIUM® (risendronate/calcium)</td>
</tr>
<tr>
<td>FOSAMAX® PLUS D (alendronate/vitamin D)</td>
<td>BONIVA® (ibandronate)</td>
</tr>
<tr>
<td>MIACALCIN® (calcitonin)</td>
<td>DIDRONEL® (etidronate)</td>
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<tr>
<td>FORTICAL® (calcitonin)</td>
<td>FORTEO® (teriparatide)</td>
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</tbody>
</table>

*Quantity Limits*
- Actonel®: 5 mg, 30 mg = 1/day; 35 mg = 4/month
- Actonel with Calcium®: 28 (4 Actonel, 24 calcium carbonate)/month
- Boniva®: 1/month
- Fosamax®: 5 mg, 10 mg, 40 mg= 1/day; 35 mg, 70 mg = 4/month
- Fosamax plus D®: 4/month
- Evista®: 1/day
- Miacalcin®: 2/month
**ENDOCRINE AGENTS**

**Clinical Criteria for Forteo® (teriparatide):**

- Forteo® (teriparatide) will be approved for individuals at high risk for fracture, with a T-score below -2 SD, who:
  - have experienced an insufficient response or intolerance to an adequate trial of a bisphosphonate, OR
  - have a contraindication to bisphosphonate use plus a history of osteoporotic fracture.

**COMMITTEE VOTE:**

- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION

**References**