Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

August 30, 2012
Responsibilities of the TennCare Pharmacy Advisory Committee

Source: Tennessee Code/Title 71 Welfare/Chapter 5 Programs and Services for Poor Persons/Part 24 Tennessee TennCare Pharmacy Advisory Committee/71-5-2401 through 71-5-2404.

- Make recommendations regarding a preferred drug list (PDL) to govern all state expenditures for prescription drugs for the TennCare program.
  - The TennCare Pharmacy Advisory Committee shall submit to the bureau of TennCare both specific and general recommendations for drugs to be included on any state PDL adopted by the bureau. In making its recommendations, the committee shall consider factors including, but not limited to, efficacy, the use of generic drugs and therapeutic equivalent drugs, and cost information related to each drug. The committee shall also submit recommendations to the bureau regarding computerized, voice, and written prior authorization, including prior authorization criteria and step therapy.
  - The state TennCare pharmacy advisory committee shall include evidence-based research in making its recommendations for drugs to be included on the PDL.
  - The TennCare bureau shall consider the recommendations of the state TennCare pharmacy advisory committee in amending or revising any PDL adopted by the bureau to apply to pharmacy expenditures within the TennCare program. The recommendations of the committee are advisory only and the bureau may adopt or amend a PDL regardless of whether it has received any recommendations from the committee. It is the legislative intent that, insofar as practical, the TennCare bureau shall have the benefit of the committee’s recommendations prior to implementing a PDL or portions thereof.
- Keep minutes of all meetings including votes on all recommendations regarding drugs to be included on the state preferred drug list
- The chair may request that other physicians, pharmacists, faculty members of institutions of higher learning, or medical experts who participate in various subspecialties act as consultants to the committee as needed.
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.

**LENGTH OF AUTHORIZATIONS:** Dependent upon diagnosis and length of therapy needed to treat. (Most medications 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 is organized into the following sections, when applicable:

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

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

---

¹ AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
BACKGROUND

- Iron overload, a response to increased iron entry into the body, can occur by the following three mechanisms: a massive increase in iron intake, an increase in iron absorption when iron intake is normal, and the parenteral administration of iron. Specifically, iron overload secondary to multiple blood transfusions may develop in patients with sickle cell disease, β thalassemia major, refractory aplastic anemia, myelodysplastic syndrome, and various leukemic states. Because there is no normal mechanism to increase iron excretion, if treatment of iron overload is deemed necessary, an iron chelator must be used. Included in this review are the orally available iron chelators, deferasirox and deferiprone.

- Both deferasirox and deferiprone are orally active chelating agents that have an affinity for iron. In addition to having an affinity to iron, these agents have a lower binding affinity to other metals such as aluminum, zinc, and copper; however, the clinical significance of the lower binding affinity is uncertain.

- Deferasirox is FDA-approved for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. Deferiprone is FDA-approved for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

- The oral iron chelators are both commonly associated with the adverse effects of abdominal pain, nausea and vomiting. Deferasirox is also commonly associated with rash, diarrhea, proteinuria, and increased serum creatinine. Less common, but severe adverse effects include dehydration, agranulocytosis, gastrointestinal hemorrhage, thrombocytopenia, drug-induced hepatitis, renal failure, and hearing loss. Deferiprone is commonly associated with abnormal neutrophil counts, elevated liver enzymes, arthralgia and abnormal urine color. Less common, but severe adverse effects include Henoch-Schonlein purpura, urticaria, periorbital edema with skin rash, heart failure, Torsades de pointes, agranulocytosis, and renal failure.

- Deferasirox carries a black box warning regarding the risks of renal impairment, including failure, hepatic impairment, including failure, and gastrointestinal hemorrhage. In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndrome, underlying renal or hepatic impairment, or low platelet counts (<50 x 10^9/L). Deferiprone carries a black box warning regarding the risk of agranulocytosis that can lead to serious infections and death.

- Deferasirox is contraindicated with creatinine clearance <40 mL/minute or serum creatinine greater than two times the age-appropriate upper limit of normal, poor performance status and high-risk myelodysplastic syndromes or advanced malignancies, and low platelet counts (<50 x 10^9/L).

- There have been post-marketing reports of cytopenias, some of which were fatal, including agranulocytosis, neutropenia, and thrombocytopenia, in patients receiving oral iron chelators. Serious hypersensitivity reactions have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Based on evidence of genotoxicity and developmental toxicity in animal studies; deferiprone can cause fetal harm when administered to a pregnant women. If deferiprone is used during pregnancy or if the patient becomes pregnant while taking deferiprone, the patients should be apprised of the potential hazard to the fetus. Women of reproductive potential should be advised to avoid pregnancy when receiving deferiprone.

- Concomitant administration of deferasirox with cholestyramine or rifampin may result in decreased deferasirox plasma concentrations decreasing the pharmacologic effects.
Deferasirox and deferiprone have both demonstrated safety and efficacy in the management of iron overload in clinical trials. With regards to deferasirox, treatment has been shown to reduce liver iron concentration and ferritin levels. Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed. Similarly, approval of deferiprone was based on a reduction in ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.

One multicenter, retrospective trial compared deferasirox, deferiprone and deferoxamine in 155 patients with thalassemia major. Deferiprone was associated with significantly greater improvements in cardiac function compared to both deferasirox and deferoxamine; however, decreases in liver iron concentrations were significantly greater with deferoxamine compared to both deferiprone and deferasirox. Deferasirox and deferiprone achieved comparable ferritin levels by trial end and both were significantly higher than deferoxamine.

According to the Study of Thalassemia and Hemoglobinopathies guideline for heart complications in thalassemia major, the choice of iron chelator for the prevention of iron-induced cardiac dysfunction must be individualized. The decision should be based on intolerance, compliance, and onset of side effects. Before starting treatment, it is recommended to have a ferritin level around 1,000 μg/dL or a liver iron concentration between 3.2 and 7 mg Fe/g dw. According to the American Association for the Study of Liver Diseases, iron chelation with either deferoxamine or deferasirox is recommended for the treatment of secondary iron overload.

RECOMMENDATION
Deferasirox and deferiprone are orally active chelating agents that have an affinity for iron. Deferasirox is FDA-approved for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. Deferiprone is FDA-approved for the treatment of patients with transfusional iron overload due to thalassemia syndromes. Both oral iron chelators have demonstrated safety and efficacy in the management of iron overload based on a reduction in ferritin levels; however, both agents also carry black box warnings regarding their use. Due to their specific FDA-approved indications as well as significant safety concerns, it is recommended all agents in this class should be subject to clinical criteria.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED WITH MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Exjade® (deferasirox)</td>
</tr>
<tr>
<td></td>
<td>Ferriprox® (deferiprone)</td>
</tr>
</tbody>
</table>
## MISCELLANEOUS AGENTS

### Clinical Criteria for Exjade®

Exjade® will be approved for recipients two years of age and older who meet ALL of the following criteria: have diagnosis of chronic iron overload due to blood transfusions. The type of anemia should be noted (i.e. Diamond-Blackfan anemia, Myelodysplastic syndrome, sickle cell anemia, β-thalassemia).  
- Diagnosis of chronic iron overload due to blood transfusions, AND
- Therapy should be initiated when:
  - Patient has received approximately 100mL/kg of PRBC, AND
  - Serum ferritin concentration is consistently > 1,000 mcg/L, OR
  - Liver iron concentration between 3.2 and 7 mg Fe/g dw L
    - This should be documented prior to the first approval.
    - Serum ferritin should be monitored monthly and documented upon prior authorization request for subsequent renewals.

**Note:** Exjade® will not be approved for recipients with creatinine clearance less than 40 mL/min or for recipients with platelet count less than 50x10⁹/L.

**Note:** It is recommended that if the serum ferritin is consistently < 500mcg/L therapy should be stopped; however, this may be up to the prescriber’s discretion in his/her experience of treating patients with iron-overload.

### COMMITTEE VOTE:

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

### Clinical Criteria for Ferriprox®

Ferriprox® will be approved for recipients who meet ALL of the following criteria: Recipient must be > two years old and have diagnosis of chronic iron overload due to blood transfusions. The type of anemia should be noted (i.e. Diamond-Blackfan anemia, Myelodysplastic syndrome, sickle cell anemia, β-thalassemia). Therapy should be initiated when:
- Diagnosis of transfusional iron overload due to thalassemia syndromes, AND
- Patient has received approximately 100mL/kg of PRBC, AND
- Serum ferritin concentration is consistently > 1000mcg/L, OR
- Liver iron concentration between 3.2 and 7 mg Fe/g dw L
  - This should be documented prior to the first approval.
  - Serum ferritin should be monitored monthly and documented upon prior authorization request for subsequent renewals.

**Note:** It is recommended that if the serum ferritin is consistently < 500mcg/L therapy should be stopped; however, this may be up to the prescriber’s discretion in his/her experience of treating patients with iron-overload.

### COMMITTEE VOTE:

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

### References

RE-REVIEW: GROWTH HORMONE AGENTS

BACKGROUND

- Growth hormone (GH) affects many metabolic processes carried out by somatic cells, which includes cells of internal organs, skin, bones, blood and connective tissues. Physiological effects of GH include stimulation of skeletal, connective tissue, muscle, organ growth and regulation of metabolism.
- Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A clinical diagnosis is based on physical growth features; therefore, a patient's growth patterns are compared to the established norms. The clinical manifestations of GHD will vary depending on whether a patient has complete or partial deficiency. GHD may also occur in adult patients; but the role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. However, GH therapy may be considered in adult patients with severe clinical manifestations and evidence of GHD due to organic disease of childhood-onset or adult-onset.
- Somatropin binds to growth hormone (GH) receptors and produces a variety of physiologic effects that can be classified as being direct or indirect. The direct effects include binding of GH to its receptor on target cells, such as adipocytes to stimulate triglyceride hydrolysis in adipose tissue, antagonism of the peripheral action of insulin and subsequent stimulation of insulin secretion, production of insulin-like growth factors (IGFs) in the liver and other tissues. The indirect effects involve secretion of IGF which acts as a direct stimulator of cell proliferation and growth. In addition to increasing linear growth, somatropin also promotes lean tissue growth, and increases bone density, protein, carbohydrate, lipid and mineral metabolism.
- GH is available as somatropin, a recombinant human GH that may be administered as a subcutaneous injection. Somatropin is Food and Drug Administration (FDA) approved for use in patients with GHD and a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, small for gestational age (SGA), Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature. Specifically, Serostim® (somatropin) is only FDA approved for the treatment of human immunodeficiency virus (HIV)-associated wasting or cachexia in adults. While Zorbtive® (somatropin) is FDA approved primarily for the treatment of short bowel syndrome in patients receiving specialized nutritional support.
- Somatropin is contraindicated in patients with the following conditions:
  - Active malignancy
  - Diabetic retinopathy
  - Acute critical illness due to surgery, trauma, or acute respiratory failure
  - Prader-Willi Syndrome patients who are severely obese or severe respiratory impairment
  - Patients with closed epiphyses
- The most common adverse events experienced with the use of somatropin include: arthralgia, peripheral edema, fluid retention, myalgia, headache, hypothyroidism, and hyperglycemia (i.e. decreased insulin sensitivity). Rare cases of pancreatitis have been reported in both pediatric and adult patients receiving somatropin and should be considered in patients who develop severe abdominal pain.
- Head-to-head comparative trials among the GH products are limited and have demonstrated no differences in safety and efficacy with the different GH preparations for the treatment of pediatric GHD.
  - Shih et al performed a randomized controlled trial that evaluated Genotropin® vs. Humatrope® vs. Saizen® in prepubertal pediatric patients with GHD. The study included 15 patients over a 12 month time period.
    - Primary endpoint: change in bone age, height velocity and height SDS (standard deviation score)
Average bone age: increased by 0.8±0.2 years for the Genotropin® group, 0.8±0.7 years for the Humatrope® group and 2.1±1.3 years in the Saizen® group.

Mean height velocity: increased from 3.4±0.7 to 11.3±2.0 cm/year with Genotropin®, from 4.0±1.3 to 9.4±1.9 cm/year with Humatrope® and from 3.7±1.2 to 11.1±3.3 cm/year with Saizen®.

Height SDS: increased from -4.0±0.5 to -2.7±0.7 in the Genotropin® group, from -2.9±0.7 to -2.2±1.0 in the Humatrope® group and -4.2±3.1 to -3.1±2.9 in the Saizen® group.

There were no differences among the three treatment groups with regard to change in bone age, height velocity and height SDS (P values not reported).

- The 2010 National Institute for Health and Clinical Excellence guidelines for the treatment of growth failure in children recommends somatropin as a treatment option with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at 4 years of age or later and Short Stature Homeobox-containing gene deficiency. Additionally, treatment with somatropin should be discontinued if any of the following apply:
  - Growth velocity increase is <50% from baseline in the first year of treatment.
  - Final height approached and growth velocity is <2 cm in one year.
  - Huge problems with adherence.
  - Final height is attained.

- The American Association of Clinical Endocrinologists (AACE) published updated guidelines in 2009 for growth hormone use in GHD adults and state that GH is recommended for the approved uses of the drug in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.
  - Patients with childhood-onset GHD previously treated with GH in childhood should be retested after final height is achieved and GH therapy should be discontinued at least one month to determine status before considering restarting therapy.
  - Patients with irreversible hypothalamic-pituitary structural lesions and patients with evidence of panhypopituitarism (at least three pituitary hormone deficiencies) and serum IGF-1 levels below the age and sex appropriate reference range off GH therapy do not require further testing.
  - For patients that received childhood GH therapy for conditions other than GHD such as Turner’s syndrome, retesting and GH therapy is not recommended after final height has been achieved.
  - There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and whether or not the product requires refrigeration; therefore, the use of one commercial GH preparation over another is not recommended.

- The 2003 AACE medical guidelines update for growth hormone use in adults and children state that most children born with SGA (small for gestational age), achieve catch-up growth in length during the first 6 to 12 months of life. If they have not caught up by 2 years of age, they are unlikely to do so in the future. Treatment at the recommended dosage usually stimulates substantial catch-up growth during the first 2 years of treatment.
RECOMMENDATION
Growth hormone (GH) affects many metabolic processes including cells of internal organs, skin, bones, blood and connective tissues. Somatropin is available as a recombinant human GH and is Food and Drug Administration (FDA) approved for use in patients with growth hormone deficiency (GHD) and a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, small for gestational age (SGA), Prader-Willi syndrome, mutations in the Short Stature Homeobox gene (SHOX) and Noonan syndrome. Somatropin growth hormone products differ in their FDA approved indications and recommended doses but clinical evidence has shown these agents exhibit similar efficacy and safety. Clinical guidelines from the American Association of Clinical Endocrinologists (AACE) state there is no evidence that one agent is more advantageous over another and do not differentiate between the various GH products. Therefore, all agents within the class can be considered therapeutic alternatives to one another. Additionally, given the potential for misuse and high cost of these agents, it is recommended that the growth hormone agents be subject to clinical criteria to ensure appropriate use.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin®</td>
<td>Humatrope®</td>
</tr>
<tr>
<td></td>
<td>Norditropin®</td>
</tr>
<tr>
<td></td>
<td>Nutropin®</td>
</tr>
<tr>
<td></td>
<td>Nutropin AQ®</td>
</tr>
<tr>
<td></td>
<td>Omnitrope®</td>
</tr>
<tr>
<td></td>
<td>Saizen®</td>
</tr>
<tr>
<td></td>
<td>Serostim®</td>
</tr>
<tr>
<td></td>
<td>Tev-Tropin®</td>
</tr>
<tr>
<td></td>
<td>Zorbtive®</td>
</tr>
</tbody>
</table>
## Clinical Criteria for Growth Hormone Agents

### For patients <= 21 years old:
will be approved if ANY of the following criteria are met:

- Patient has a diagnosis of short stature associated with Turner’s Syndrome, Noonan Syndrome or mutations of the Short Stature Homeobox (SHOX) gene
- Patient has a diagnosis of Prader-Willi Syndrome;
- Patient has evidence of hypothalamic-pituitary disease or structural lesions/trauma to the pituitary, including pituitary tumor, pituitary surgical damage, trauma, or cranial irradiation and meets any of the following:
  - Failed a GH stimulation test (peak GH level <10ng/mL)
  - Documented low IGF-1 level (below normal for patient’s age)
  - Has deficiencies in 3 or more pituitary axes
- Patient has chronic renal insufficiency (CrCl < 30mL/min/1.73m2)
- Patient is a newborn infant and has evidence of hypoglycemia AND either a low GH level (<20 ng/mL) or a low for age IGF-1/IGF Binding Protein #3 level
- Patient has failed two GH stimulation tests (defined as peak GH level < 10 ng/mL), OR has failed one GH stimulation test and has a documented low IGF-1 level based on age normal values.
  - Continuation of GH therapy will be approved only if height velocity is within range of normal for patient’s age or bone age.
  - Therapy will not be approved once epiphyseal fusion occurs.
  - For recipients who have been on GH prior to the start of this edit, the requirement for 2 stimulation tests will be waived.
- Diagnosis of Small for Gestational Age (SGA) or Intrauterine Growth Retardation (IGR), > 2 years old, and has a height at least 2 standard deviations below the population mean for age
- Patient has a diagnosis of HIV/AIDS wasting/cachexia
- Patient has short bowel syndrome and is receiving specialized nutrition support.

**NOTE:** GH therapy will NOT be approved for idiopathic short stature.

### Patients > 21 years old:
will be approved for ANY of the following:

- Patient has evidence of hypothalamic-pituitary disease or structural lesions/trauma to the pituitary, including pituitary tumor, pituitary surgical damage, trauma, or cranial irradiation (can be diagnosed either in childhood or adulthood) AND meets any one of the following:
  - Failed at least one GH stimulation test
  - Has at least one documented low IGF-1 level
  - Has deficiencies in 3 or more pituitary axes

**NOTE:** For recipients diagnosed in childhood with hypothalamic-pituitary disease or structural lesions/trauma to the pituitary who have a past history of GH use, no retesting is necessary.

- Failure of two GH stimulation tests (peak GH level < 5 ng/mL) or failure of one GH stimulation test and documented low IGF-1
- Patient has a diagnosis of HIV/AIDS wasting/cachexia
- Patient has short bowel syndrome and is receiving specialized nutrition support.

## COMMITTEE VOTE:

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

## References


---

**RE-REVIEW: INSULIN-LIKE GROWTH FACTOR-1**

**BACKGROUND**

- Insulin-like growth factor (IGF-1) is the primary mediator of growth hormone and has many actions in the body including the promotion of skeletal, organ, and other tissue growth, suppression of hepatic glucose production, inhibition of insulin secretion, maintenance and regeneration of the nervous system. Growth Hormone (GH) binds to GH receptors and stimulates growth by acting on the liver and growth plate. In the liver, GH stimulates the synthesis and release of IGF-1. At the growth plate, GH triggers the proliferation and differentiation of prechondrocytes into chondrocytes and the production of IGF-1. Then, IGF-1 stimulates chondrocyte expansion and maturation, thus causing cartilage growth.

- Currently, Increlex® (mecasermin) is the only insulin-like growth factor-1 (IGF-1) product available. Increlex® is FDA approved for the treatment of growth failure in children with severe primary IGF-1 deficiency or in children with growth hormone gene deletion who have developed neutralizing antibodies to GH.

- The most common and serious adverse events associated with the use of mecasermin include: reactions at the injection site, lipohypertrophy, hypertrophy of tonsils, hypoglycemia, immune hypersensitivity reaction, raised intracranial pressure, seizure and dyspnea.

  - Mecasermin should be administered via subcutaneous administration only; intravenous administration of mecasermin is contraindicated. Other contraindications include:
    - patients with benzyl alcohol hypersensitivity, as Increlex® contains benzyl alcohol as a preservative.
    - patients with active or suspected neoplastic disease. Administration in patients with concurrent neoplastic disease may result in an increase in tumor size and disease progression. Additionally, therapy should be discontinued if there is evidence of a neoplasm.
    - patients with closed epiphyses.

---

- Mecasermin should be used cautiously in patients with diabetes mellitus or history of hypoglycemia. Also, due to the insulin-like hypoglycemic effects, mecasermin should be administered shortly before or after a snack and should not be given when a meal or snack is omitted. Glucose monitoring and IGF-1 dose titration are recommended until a well-tolerated dose is established.

  - There are no known drug interactions documented with mecasermin.

  - A double-blind randomized placebo-controlled trial that evaluated 17 pediatric patients with severe primary IGF-1 deficiency showed that at six months, height velocity increased by 5.9 cm/year with IGF-1 therapy compared to an increase of 1.6 cm/year with placebo. Patients in the placebo group had an increase in
height velocity by 5.9 cm/year compared to baseline after switching to IGF-1 therapy for six months.

- Currently, there are no consensus guidelines available for the management of primary insulin-like growth factor-1 (IGF-1) deficiency. However, current literature supports the use of IGF-1 only in the FDA approved indications with lack of data to support efficacy and safety of IGF-1 therapy in children with idiopathic short stature.

RECOMMENDATION

Increlex® (mecasermin) is the only recombinant human insulin-like growth factor-1 (IGF-1) and is FDA approved for the treatment of growth failure in pediatric patients with severe primary IGF-1 deficiency and in those with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Although there are no consensus guidelines on the management of primary IGF-1 deficiency, the literature supports the use of IGF-1 in the FDA-approved indications. Therefore it is recommended mecasermin should be subject to clinical criteria to ensure appropriate use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: INSULIN-LIKE GROWTH FACTOR-1

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increlex® (mecasermin)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Clinical Criteria for Increlex® (mecasermin)

Will be approved for patients <21 years old with a diagnosis of:
- Growth failure due to severe primary IGF-1 deficiency (documentation of low-IGF-1 must be provided), OR
- Growth hormone gene deletion in a patient who has developed neutralizing antibodies to growth hormone (GH).

Note: Will not be approved for individuals with closed epiphyses

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References


RE-REVIEW: AGENTS FOR ACROMEGALY

BACKGROUND

- Acromegaly is a long-term condition characterized by growth hormone (GH) hypersecretion. The mean age at diagnosis is around 40-45 years of age. In general, the onset of the disease is gradual and slowly progresses. The most common cause of
acromegaly is a GH secreting adenoma of the anterior pituitary (also known as a somatotroph). The clinical manifestations may include thickened skin, enlarged hands, feet, jaw and forehead. Other clinical effects may include arthritis and depending on the size of the adenoma, symptoms such as headaches and vision loss can occur. Mortality from cardiovascular disease and cancer is common in patients with Acromegaly.

- The goals of treatment include normalization of biochemical variables, reversal of tumor mass effects, minimizing long-term mortality risk, improving signs, symptoms and comorbidities of the disease. Target concentrations of GH and IGF-1 in patients with acromegaly are <1 ng/mL and levels within the reference range for the patient’s age and gender. With normalization of IGF-1 (insulin-like growth factor) concentrations, the life expectancy is similar to that of the general population. Treatment options for acromegaly patients include surgery, medical therapy, and radiotherapy. Medical therapy options include the following drug classes: somatostatin analogs, dopamine agonists, and GH receptor antagonists. Medical therapy is typically utilized when surgery alone does not achieve GH and IGF-1 target concentrations. The role of medical therapy as primary treatment for acromegaly has not been clearly established, but does play a role in this setting in patients with unacceptable surgical risks, patients who refuse surgery, and patients who have an adenoma that is unlikely to be cured surgically.

- This class review will primarily focus on the somatostatin analogs (lanreotide and octreotide) and the GH receptor antagonist (GHRA), pegvisomant. The somatostatin analogs directly inhibit GH secretion and control both GH and IGF-1 levels. The GHRA directly blocks peripheral GH-dependent release of IGF-1, which mediates most of the actions of GH.

- All of the acromegaly agents are Food and Drug Administration (FDA)-approved for the treatment of acromegaly in patients who have had an inadequate response to or cannot tolerate surgery or radiotherapy. Furthermore, octreotide and pegvisomant are approved for use in acromegalic patients who have failed or who cannot tolerate other medical therapies. Octreotide has an additional FDA-approved indication for use as symptomatic treatment of neuroendocrine carcinomas.

- The most common and severe adverse events for the acromegaly agents include:
  - **lanreotide**: bradycardia, injection site reactions, abdominal pain, cholelithiasis, flatulence, nausea, anemia and pancreatitis.
  - **octreotide**: abdominal discomfort/pain, diarrhea, carcinoid or vasoactive intestinal peptide tumors, flatulence, nausea, dizziness, backache, fatigue, bradycardia, cardiac dysrhythmia, congestive heart failure, hyperglycemia, hypoglycemia, hypothyroidism and ascending cholangitis.
  - **pegvisomant**: injections site reaction, diarrhea, nausea, infections, influenza-like illness and pain, chest pain and hepatitis.

  o **Contraindications/Precautions:** (See MedMetric Class Review, pg. 25, table 8)
    - **lanreotide**: should be initiated with caution in patients with underlying cardiac disease due to decreases in heart rate that may cause sinus bradycardia. Lanreotide has been shown to inhibit the secretion of insulin and glucagon; patients may experience either hypoglycemia or hyperglycemia, so blood glucose concentrations should be monitored in all patients. Patients with pre-existing gallbladder disease may experience gallstone formation as lanreotide may reduce gallbladder motility. Thyroid function tests are recommended when clinically indicated as decreases in thyroid function have occurred during therapy. Lastly, dosage adjustment is required in patients with moderate to severe hepatic and/or renal dysfunction.
    - **octreotide**: should be used with caution in patients with gallbladder disease because octreotide may increase the risk of acute cholecystitis, ascending cholangitis, biliary obstruction or cholestatic hepatitis. It has also been shown to alter the absorption of dietary fats in some patients. Acromegaly patients, as a result of their underlying disease and/or subsequent treatment, are at an increased risk of developing diabetes.
Baseline and periodic assessment of thyroid function is recommended during chronic therapy, as octreotide suppresses the secretion of thyroid stimulating hormone which may result in hypothyroidism or goiter. Additionally, vitamin B12 deficiency and abnormal Schilling tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B12 levels is recommended for patients receiving chronic therapy. Also, patients with renal failure requiring dialysis and patients with liver cirrhosis will require a dose adjustment.

- **Pegvisomant:** all patients with neoplastic disease tumors being treated with pegvisomant should be carefully monitored with periodic imaging scans to prevent progressive tumor growth. Furthermore, glucose tolerance may increase in some patients being treated with pegvisomant, as growth hormone decreases insulin sensitivity by opposing the effects of insulin on carbohydrate metabolism.
  - There are no clinically significant drug interactions associated with the acromegaly agents.

- Lanreotide, octreotide, and pegvisomant have all demonstrated efficacy in the treatment of acromegaly. Specifically, treatment suppresses growth hormone and insulin-like growth factor 1 concentrations within normal limits and improves symptoms. Head-to-head trials comparing the long-acting formulations of lanreotide and octreotide do not reveal consistent superiority of one agent over another. Additionally, clinical trial data supports the use of octreotide for symptomatic management of neuroendocrine tumors. The PROMID trial suggests that octreotide has the ability to significantly prolong the time to tumor progression and reduce overall mortality compared to placebo.
  - A randomized trial performed by Madsen et al evaluated Somatostatin analogs, lanreotide long-acting (80mg Q4 weeks) or octreotide long acting (10 to 30 mg Q4) weeks versus pegvisomant plus somatostatin analogs at half the usual dosage over 24 weeks.
    - No differences in IGF-1 concentrations were noted between the two treatments after 24 weeks (221±17 vs 189±30 μg/L; P=0.48), as well as the baseline change in IGF-1 concentrations between the two treatments (P=0.15).
    - There was no difference between the treatments with regard to glucose, lipid, or protein oxidation rates. Additionally, the two treatments were comparable after 24 weeks of treatment in terms of body weight, bone mineral content, fat mass, lean body mass and fat percentage.

- The 2011 American Association of Clinical Endocrinologists (AACE) guidelines for the diagnosis and treatment of Acromegaly state:
  - There is sufficient evidence to recommend surgery as the primary therapy for all patients with macroadenomas. Surgery is indicated for all patients with macroadenoma and mass effects, including visual loss.
  - In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention.
  - Pituitary radiation therapy in acromegaly should be considered an adjunctive treatment in patients not fully responding to surgical or medical treatments (or both).
  - Somatostatin analogs are effective in normalizing IGF-1 and GH levels in approximately 55% of patients and reduce pituitary tumor size modestly in approximately 25 to 70% of patients, depending on whether they are used as adjuvant or de novo therapy, respectively.
  - Pegvisomant is highly effective in normalizing IGF-1 values (>90%), including patients who are partially or completely resistant to other medical therapies. In patients with a partial response to somatostatin analog therapy, the addition of daily, weekly, or twice weekly pegvisomant may be beneficial.
ENDOCRINE & METABOLIC AGENTS

RECOMMENDATION

Acromegaly is a long-term condition characterized by growth hormone (GH) hypersecretion, multisystem-associated morbidities, increased mortality and is most commonly caused by a GH secreting adenoma. Treatment goals include normalization of biochemical variables, reversal of mass effects of the tumor, minimizing long-term mortality risk, improving signs, symptoms and comorbidities of the disease. All of the acromegaly agents are Food and Drug Administration (FDA)-approved for the treatment of acromegaly in patients who have had an inadequate response to or cannot tolerate surgery or radiotherapy. Furthermore, octreotide and pegvisomant are approved for use in acromegalic patients who have failed or who cannot tolerate other medical therapies. Octreotide has an additional FDA-approved indication for use as symptomatic treatment of neuroendocrine carcinomas. The AACE guidelines for acromegaly recommend somatostatin analogs as first-line pharmacologic therapy, with pegvisomant reserved for individuals who fail to respond to somatostatin analogs. Based on this information, pegvisomant should be considered second-line therapy behind the somatostatin analogs.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

RE-REVIEW: AGENTS FOR ACROMEGALY

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>octreotide (compares to Sandostatin®)</td>
<td>Sandostatin® (octreotide)</td>
</tr>
<tr>
<td>Sandostatin LAR® (octreotide long-acting)</td>
<td>Somatuline LAR® (lanreotide long acting)</td>
</tr>
<tr>
<td></td>
<td>Somavert® (pegvisomant)</td>
</tr>
</tbody>
</table>

References


RE-REVIEW: BONE: BISPHOSPHONATES

BACKGROUND

- Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility
and consequent susceptibility to fracture. According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis, which includes the use of bisphosphonates, is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient’s quality of life.

- Bisphosphonates inhibit osteoclast activity by binding to bone surfaces that are undergoing active bone resorption resulting in the impairment of the ability for osteoclasts to form the ruffled border, adhere to the bony surface, and produce the protons necessary to continue bone resorption.

- In general, the bisphosphonates are FDA-approved for the prevention and/or treatment of osteoporosis in postmenopausal women, in men, and in patients taking prolonged courses of glucocorticoids. However, etidronate is only FDA-approved for the prevention and treatment of heterotropic ossification and for the treatment of Paget’s Disease. Tiludronate is only FDA-approved for the treatment of Paget’s Disease. Alendronate and risedronate are also FDA-approved for the treatment of Paget’s Disease.

- The most common adverse events associated with bisphosphonates are related to the gastrointestinal tract and include abdominal pain, constipation, diarrhea, dyspepsia, nausea and vomiting. Musculoskeletal pain and bone pain are also commonly associated with the use of bisphosphonates. Less common, but severe adverse events, include esophagitis, esophageal or gastric ulcers and osteonecrosis.
  - Bisphosphonates are contraindicated with hypocalcemia or hypersensitivity to any component of selected product. Oral bisphosphonates are also contraindicated in patients who are unable to stand or sit upright for at least 30 minutes (60 minutes for ibandronate). Alendronate and etidronate are additionally contraindicated with abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia and any patient at an increased risk of aspiration (alendronate oral solution). Etidronate is also contraindicated with clinically overt osteomalacia.
  - Oral bisphosphonates are associated with a warning regarding the possibility of upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcers. Patients should be advised to pay particular attention to and be able to comply with dosing instructions to minimize the risk of adverse effects.
  - Prior to initiating therapy with bisphosphonates, hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism should be effectively treated. There have been reports of hypocalcemia following bisphosphonate dosing so it is important that serum calcium, vitamin D, and symptoms of hypocalcemia should be monitored during treatment with bisphosphonates.
  - Etidronate suppresses bone turnover, and may retard mineralization of osteoid laid down during the bone accretion process. Treatment regimens exceeding the recommended daily maximum dose or continuous administration of medication may be associated with osteomalacia and an increased risk of fracture.
  - Alendronate is not recommended for use in patients with creatinine clearance less than 35 mL/min. Ibandronate, risedronate and tiludronate are not recommended for use in patients with creatinine clearance less than 30 mL/min.
  - Absorption of bisphosphonates may be decreased by the concomitant administration of multivalent cations, including calcium, aluminum and magnesium. Dosing regimens should be modified to avoid this interaction. Concomitant administration of nonsteroidal anti-inflammatory drugs with bisphosphonates may increase the risk of gastric ulceration.

- Data from trials specifically examining fractures indicates that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo. Head-to-head trials have concluded conflicting data when comparing one bisphosphonate agent to
another in regards to efficacy. Evidence suggests that alendronate results in greater increases on BMD when compared to risedronate. Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate. Additionally, there is data to support alendronate and risedronate having similar efficacy. Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate, in one trial, while another showed ibandronate to be similar in efficacy to alendronate. Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another for the treatment and prevention of osteoporosis.

- Many clinical guidelines for osteoporosis, including the guidelines from the National Osteoporosis Foundation, focus on screening, diagnosis and appropriate selection of patients for treatment and do not specifically recommend a preferred medication or medication class. Current guidelines for the diagnosis and treatment of postmenopausal osteoporosis from the American Association of Clinical Endocrinologists state that drugs with proven anti-fracture efficacy should be used and specify alendronate, risedronate, zoledronic acid and denosumab as first-line therapy. Similarly, the North American Menopause Society states that bisphosphonates are the first-line drugs for treating postmenopausal women with osteoporosis due to their proven efficacy in reducing the risk of vertebral and non-vertebral fractures.

**RECOMMENDATION**

In general, the bisphosphonates are FDA-approved for the prevention and/or treatment of osteoporosis in postmenopausal women, in men, and in patients taking prolonged courses of glucocorticoids; however, some agents are also approved for the treatment of Paget’s disease. Data from trials specifically examining fractures indicates that the use of bisphosphonates is efficacious and significantly lowers the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas. Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one bisphosphonate is more efficacious for the treatment and prevention of osteoporosis. While not all clinical guidelines for osteoporosis recommend a preferred medication and/or medication class, the American Association of Clinical Endocrinologist and the North American Menopause Society recommend bisphosphonates as first-line therapy for the treatment of osteoporosis in postmenopausal women. Bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis due to the good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures. Therefore, it is recommended at least one bisphosphonate should be available for use, which should be approved for use in men, postmenopausal women and for the treatment of Paget’s Disease.

**COMMITTEE VOTE:**

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

**RE-REVIEW: BONE: BISPHOSPHONATES**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate QL (compares to Fosamax®)</td>
<td>Actonel® QL (risedronate)</td>
</tr>
<tr>
<td>Atelvia® QL (risedronate)</td>
<td>Boniva® QL (ibandronate)</td>
</tr>
<tr>
<td>Diclase® (etidronate)</td>
<td>etidronate (compares to Diclase®)</td>
</tr>
<tr>
<td>Fosamax® QL (alendronate)</td>
<td>Fosamax Plus D® QL (alendronate/cholecalciferol)</td>
</tr>
<tr>
<td>ibandronate QL (compares to Boniva®)</td>
<td>Skelid® QL (tiludronate)</td>
</tr>
</tbody>
</table>
Quantity Limits:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate</td>
<td>5mg, 10 mg, 40 mg: 1 per day</td>
</tr>
<tr>
<td></td>
<td>35 mg, 70 mg: 4 per 28 days</td>
</tr>
<tr>
<td>Actonel®</td>
<td>5 mg, 30 mg: 1 per day</td>
</tr>
<tr>
<td></td>
<td>35 mg: 4 per 28 days</td>
</tr>
<tr>
<td></td>
<td>75 mg: 2 per month</td>
</tr>
<tr>
<td></td>
<td>150 mg: 1 per month</td>
</tr>
<tr>
<td>Atelvia®</td>
<td>4 per 28 days</td>
</tr>
<tr>
<td>Boniva ®</td>
<td>1 per month</td>
</tr>
<tr>
<td>Fosamax®</td>
<td>5mg, 10 mg, 40 mg: 1 per day</td>
</tr>
<tr>
<td></td>
<td>35 mg, 70 mg: 4 per 28 days</td>
</tr>
<tr>
<td>Fosamax Plus D®</td>
<td>4 per 28 days</td>
</tr>
<tr>
<td>ibandronate</td>
<td>1 per month</td>
</tr>
<tr>
<td>Skelid®</td>
<td>2 per day</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

| APPROVED | DISAPPROVED | APPROVED with MODIFICATION |

References


RE-REVIEW: BONE: SERMs

BACKGROUND

- This class review will focus on raloxifene which is the only selective estrogen receptor modulator (SERM) available for the management of osteoporosis.
- SERMs demonstrate both estrogenic and anti-estrogenic activity in specific tissues within the body. Raloxifene acts as an estrogen agonist on bone and lipid metabolism, and as an estrogen antagonist on breast and endometrial tissue.
- Raloxifene is FDA-approved for the prevention and treatment of osteoporosis in postmenopausal women, as well as for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with osteoporosis who are at high risk for invasive breast cancer.
- Hot flashes and leg cramps are the adverse effects most commonly associated with the use of raloxifene. Less commonly, thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism (PE) and stroke have been associated with the use of raloxifene.
Raloxifene carries a boxed warning regarding an increased risk of venous thromboembolism (VTE) and death caused by stroke; therefore patients with an active VTE or a history of VTE should not receive raloxifene.

- Raloxifene is contraindicated with active or past history of VTE, including DVT, PE, and retinal vein thrombosis. In addition, raloxifene is contraindicated with pregnancy, in women who may become pregnant, and in nursing mothers.
- There is no indication for premenopausal use of raloxifene; safety of raloxifene in premenopausal women has not been established and its use is not recommended. Raloxifene has not been adequately evaluated in women with a prior history of breast cancer, and there is no indication for the use of raloxifene in men.
- Limited clinical data suggest that some patients with a history of marked hypertriglyceridemia (>500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with raloxifene. Women with this medical history should have serum triglycerides monitored when taking raloxifene.

- There are no clinically significant drug interactions associated with raloxifene.

- Data from placebo-controlled trials consistently demonstrate that raloxifene significantly increases bone mineral density (BMD) in postmenopausal women with osteoporosis. There is also data demonstrating a reduction in the risk of vertebral fractures with raloxifene compared to placebo; however, raloxifene has not been demonstrated to reduce non-vertebral or hip fractures. Head-to-head trial data with other agents for the treatment of osteoporosis are limited; however, increases in BMD appear to be significantly greater with alendronate compared to raloxifene.

- Raloxifene was compared to alendronate in 1,412 postmenopausal women with osteoporosis who had no previous use of any bone-active agent. There was no difference in the number of patients experiencing at least one new osteoporotic vertebral or non-vertebral fracture between raloxifene and alendronate (2.9 vs 3.1%; P value not reported). BMD at the lumbar spine, femoral neck, and total hip were significantly increased after two years (P<0.001), with significantly greater increases with alendronate at all sites compared to raloxifene (P<0.05 for all).

- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the two treatments. However, in a follow-up trial of 6.75 median years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was still no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years.

- Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options. While not every treatment guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy in the treatment of women and men with osteoporosis, and for the treatment of postmenopausal osteoporosis. With regards to SERMS, good quality evidence supports their use in reducing vertebral fractures; however, these agents have not demonstrated a reduction in non-vertebral and hip fractures. SERMS are recognized as a potential treatment option for the prevention and treatment of osteoporosis, but are recommended by the American Association of Clinical Endocrinologists as second- or third-line therapy for treatment of postmenopausal osteoporosis. According to the National Comprehensive Cancer Network, raloxifene is recognized as a potential option to reduce the risk of breast cancer; however, tamoxifen is a "superior" choice for most postmenopausal women desiring non-surgical risk reduction therapy.
RECOMMENDATION
Raloxifene is FDA-approved for the prevention and treatment of osteoporosis in postmenopausal women, as well as for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with osteoporosis who are at high risk for invasive breast cancer. Clinical trial data demonstrates that raloxifene significantly increases bone mineral density in postmenopausal women with osteoporosis as well as reducing vertebral fractures; however, raloxifene has not demonstrated a reduction in non-vertebral and hip fractures. Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options; however, the bisphosphonates are generally recognized as first-line therapy. Raloxifene is recognized as a potential treatment option for the prevention and treatment of osteoporosis, but generally is recommended as second- or third-line therapy for treatment of postmenopausal osteoporosis. According to the National Comprehensive Cancer Network, raloxifene is recognized as a potential option to reduce the risk of breast cancer; however, tamoxifen is a superior choice for most postmenopausal women. While not considered first line therapy, raloxifene is an effective treatment option for osteoporosis in postmenopausal females. In order to provide treatment options for osteoporosis with differing mechanisms of action, it is recommended raloxifene should be available for use.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

RE-REVIEW: BONE: SERMs

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evista® (raloxifene)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Quantity Limits:

<table>
<thead>
<tr>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evista®</td>
</tr>
<tr>
<td>1 per day</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

References
BACKGROUND

- This class review focuses on the available calcitonin agents. Calcitonin-salmon, a calcitonin derivative, is a polypeptide containing 32 amino acids in the same linear sequence as endogenous calcitonin. Endogenous calcitonin acts primarily on bone; however, direct renal and gastrointestinal effects have also been observed.

- Calcitonin-salmon appears to have similar actions but has a greater potency and duration of action compared to endogenous calcitonin. The actions of calcitonin on bone and its role in normal human bone physiology are not completely understood, although calcitonin receptors have been discovered in osteoclasts and osteoblasts. In addition, it is believed that these agents cause marked transient inhibition of the ongoing bone resorptive process.

- Injectable calcitonin-salmon is FDA-approved for the early treatment of hypercalcemic emergencies, for the treatment of symptomatic Paget’s disease of bone, and for the treatment of postmenopausal osteoporosis in women. Nasal calcitonin-salmon is only approved for the treatment of postmenopausal osteoporosis. Specifically, the calcitonins are for use only in postmenopausal women greater than five years postmenopause with low bone mass relative to healthy premenopausal females.

- Adverse events commonly associated with the use of calcitonin are dependent on the route of administration. Calcitonin injection is most commonly associated with nausea and injection site reactions, whereas calcitonin nasal spray is most commonly associated with rhinitis and symptoms of the nose, including dryness, irritation and itching. Because calcitonin-salmon is a polypeptide, the possibility of allergic reaction exists, and a few cases of serious allergic-type reactions have been reported in patients receiving calcitonin.

  - Treatment with injectable calcitonin-salmon may lead to hypocalcemic tetany under special circumstances although no cases have been reported. Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.
  - An increased incidence of non-functioning pituitary adenomas has been observed in a one year, rate toxicity trial. The relevance of these findings to humans is unknown.
  - There are no clinically significant drug interactions associated with calcitonin.

- Overall, there is a lack of substantial clinical trial data for this medication class, as trials are typically small in size and observational in design. Injectable calcitonin-salmon has demonstrated beneficial effects in the treatment of Paget’s disease. Treatment produced bone and symptom relief, increased mobility, and decreased alkaline phosphate and other bone turnover markers. In addition, injectable calcitonin-salmon has been shown to cause disease regression in some patients. A meta-analysis of 30 clinical trials demonstrated that calcitonin significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for non-vertebral fractures. There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments; however, available data supports the use of other osteoporosis therapies over calcitonin for increasing bone mass density (BMD).

  - Calcitonin nasal spray was compared to alendronate in 299 women who were at least 5 years postmenopause and had a diagnosis of osteoporosis. After 1 year of therapy, alendronate significantly increased BMD at the lumbar spine compared to calcitonin (5.16 vs 1.18%; P<0.001). Alendronate significantly increased BMD at the femoral neck (2.78 vs 0.58%; P<0.001) and hip trochanter (4.73 vs 0.47%; P<0.001) compared to calcitonin. Calcitonin significantly
increased BMD at the femoral neck at months six and 12 compared to placebo (P<0.001), but there was no difference at hip trochanter (P value not reported).

- Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options. While not every treatment guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy in the treatment of women and men with osteoporosis, and for the treatment of postmenopausal osteoporosis. Calcitonins are recognized as a potential option for the treatment of osteoporosis; however current guidelines from the American Association of Clinical Endocrinologists recommend calcitonin as a last line therapy for the treatment of postmenopausal osteoporosis. Similarly, the North American Menopause Society states calcitonin is not a first-line drug for postmenopausal osteoporosis treatment, as its fracture efficacy is not strong and its BMD effects are less than those of other agents.

RECOMMENDATION
Injectable calcitonin-salmon is FDA-approved for the early treatment of hypercalcemic emergencies, for the treatment of symptomatic Paget's disease of bone, and for the treatment of postmenopausal osteoporosis in women. Nasal calcitonin-salmon is only approved for the treatment of postmenopausal osteoporosis. Overall, there is a lack of substantial clinical trial data for this medication class as clinical trials are limited by small sample size and design. There is also a lack of substantial head-to-head data comparing calcitonins to other established osteoporosis treatments; however, available data supports the use of first- and second-line osteoporosis therapies over calcitonin for increasing bone mineral density. Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options; however, the bisphosphonates are generally recognized as first-line therapy. Calcitonins are recognized as a potential option for the treatment of osteoporosis, and have fair quality evidence to support their use in reducing vertebral fractures; they have not demonstrated a reduction in non-vertebral and hip fractures. Current guidelines from the American Association of Clinical Endocrinologists recommend calcitonin as a last line therapy for the treatment of postmenopausal osteoporosis. Due to the lack of substantial trial data and given that calcitonin is considered a last line therapy for the treatment of postmenopausal osteoporosis, it is recommended calcitonin should be subject to clinical criteria.

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-REVIEW: BONE: CALCITONIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PREFERRED</strong></td>
<td><strong>NON-PREFERRED</strong></td>
<td></td>
</tr>
<tr>
<td>Fortical® (calcitonin-salmon)</td>
<td>calcitonin-salmon nasal spray (compares to Miacalcin®)</td>
<td></td>
</tr>
<tr>
<td>Miacalcin® (calcitonin-salmon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quantity Limits:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin-salmon nasal spray</td>
<td>2 per month (billing units of 3.7 mL) 3.7 mL/30 days</td>
<td></td>
</tr>
<tr>
<td>Fortical®</td>
<td>2 per month (billing units of 3.7 mL) 3.7 mL/30 days</td>
<td></td>
</tr>
<tr>
<td>Miacalcin® nasal spray</td>
<td>2 per month (billing units of 3.7 mL) 3.7 mL/30 days</td>
<td></td>
</tr>
<tr>
<td>Miacalcin® injection</td>
<td>1 mL/day</td>
<td></td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>
**Clinical Criteria for Fortical®**

Fortical® will be approved for patients meeting ALL of the following criteria:

- Diagnosis of osteoporosis in postmenopausal women greater than five years postmenopause, AND
  - Trial and failure, contraindication or intolerance to BOTH bisphosphonates AND raloxifene.

**COMMITTEE VOTE:**

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

**Clinical Criteria for Miacalcin® nasal spray & calcitonin-salmon nasal spray**

Will be approved for patients meeting ALL of the following criteria:

- Diagnosis of osteoporosis in postmenopausal women greater than five years postmenopause, AND
  - Trial and failure, contraindication or intolerance to BOTH bisphosphonates AND raloxifene, AND
  - Trial and failure, contraindication or intolerance to preferred agents

**COMMITTEE VOTE:**

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

**Clinical Criteria for Miacalcin® injection**

Will be approved for patients meeting ONE of the following criteria:

- Diagnosis of Paget’s disease of the bone, OR
- Diagnosis of osteoporosis in postmenopausal women greater than five years postmenopause, AND
  - Trial and failure, contraindication or intolerance to BOTH bisphosphonates AND raloxifene, AND
  - Trial and failure, contraindication or intolerance to preferred agents

**COMMITTEE VOTE:**

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

**References**

RE-REVIEW: BONE: PARATHYROID HORMONE

BACKGROUND

- Parathyroid hormone is the primary regulator of calcium and phosphate metabolism in bone and kidney and its physiologic actions include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. Forteo® (teriparatide) is the only parathyroid hormone for the treatment of osteoporosis available.
- Teriparatide is a recombinant human parathyroid hormone and has the same physiological actions on bone and kidney as endogenous parathyroid hormone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength.
- Teriparatide is FDA-approved for use in patients at high risk for fracture specifically to increase bone mass in men with primary or hypogonadal osteoporosis, for the treatment of patients with glucocorticoid-induced osteoporosis, and for the treatment of postmenopausal women with osteoporosis.
- Adverse events most commonly associated with the use of teriparatide include nausea, arthralgia, rhinitis, pain and transient hypercalcemia. Less commonly, angina has also been associated with the use of teriparatide.
  - Teriparatide is associated with a boxed warning regarding the increased incidence of osteosarcoma and should not be prescribed for patients who are at increased baseline risk for osteosarcoma which include patients with Paget's disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation therapy involving the skeleton.
  - The safety and efficacy of teriparatide have not been evaluated beyond two years of treatment. Because of this, use of the agent for more than two years during a patients' lifetime is not recommended.
  - Patients with bone metastases, a history of skeletal malignancies, and metabolic bone diseases other than osteoporosis should not be treated with teriparatide. In addition, teriparatide has not been evaluated in patients with pre-existing hypercalcemia. These patients should not be treated with teriparatide because of the possibility of exacerbating hypercalcemia. Patients with an underlying hypercalcemic disorder (e.g., primary hyperparathyroidism) should also not be treated with teriparatide. Hypercalcemia may predispose patients to digitalis toxicity; therefore, patients receiving digoxin should use teriparatide with caution. Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.
  - There are no clinically significant drug interactions associated with the use of teriparatide.
- Teriparatide has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women. The EUROFORS trial was a prospective, two year trial in which all patients received teriparatide for the first year of treatment. After 12 months, patients were divided into two different substudies. In Substudy 1, for the second year of treatment patients were randomized to teriparatide, the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on teriparatide for the second year of treatment. After the first year of treatment, teriparatide significantly increased BMD at the lumbar spine, total hip and femoral neck. The benefits of teriparatide appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued teriparatide for a total of two years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of treatment BMD at the lumbar spine, total hip, and...
femoral neck continued to increase significantly with teriparatide. BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significant increase BMD at the femoral neck.

- Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options. While not every treatment guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy in the treatment of women and men with osteoporosis, and for the treatment of postmenopausal osteoporosis. Guidelines from both the American Association of Clinical Endocrinologists and the North American Menopause society recommend teriparatide as a potential option for the prevention and treatment of osteoporosis, but recommend that it be reserved for patients at very high fracture risk or in patients who have failed first-line bisphosphonate therapy.

**RECOMMENDATION**

Teriparatide is a recombinant human parathyroid hormone and has the same physiological actions on bone and kidney as endogenous parathyroid hormone. Teriparatide is FDA-approved for use in patients at high risk for fracture specifically to increase bone mass in men with primary or hypogonadal osteoporosis, for the treatment of patients with glucocorticoid-induced osteoporosis, and for the treatment of postmenopausal women with osteoporosis. Clinical trials evaluating the safety and efficacy of teriparatide in FDA-approved indications demonstrate that bone mineral density (BMD) is consistently increased; however, the safety and efficacy of teriparatide have not been evaluated beyond two years of treatment, and a treatment duration greater than two years in a patient’s lifetime is not recommended. Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options; however, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis. With regards to parathyroid hormones, guidelines recommend teriparatide as a potential option for the prevention and treatment of osteoporosis, but generally recommend that it be reserved for patients at very high fracture risk or in patients who have failed first-line bisphosphonate therapy. Due to the lack of long term outcomes data and safety concerns, it is recommended that teriparatide be subject to clinical criteria.

**COMMITTEE VOTE:**

APPROVED    DISAPPROVED    APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th></th>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Forteo™®</td>
<td>(teriparatide)</td>
</tr>
</tbody>
</table>

**Clinical Criteria for Forteo™:**

Will be approved for individuals at high risk for fracture, with a T-score at or below -2.5 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, AND
- Have been screened and found not to have pre-existing hyperparathyroidism.

Note: The safety and efficacy of teriparatide has not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

**COMMITTEE VOTE:**
ENDOCRINE & METABOLIC AGENTS

References

RE-REVIEW: ORAL PROGESTINS

BACKGROUND
• Endometriosis is a common, benign and estrogen-dependent condition. Some patients with endometriosis may not experience symptoms while others may experience distressing and debilitating symptoms such as pelvic pain, severe dysmenorrhea, dyspareunia and infertility. Surgical and medical treatments are available for the management of endometriosis. According to the American Society for Reproductive Medicine, oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists and anti-progestogens have all been utilized as medical treatments for endometriosis. However, there is no high quality evidence to support the superiority of one medical treatment over another. So treatment decisions are individualized based on the severity of symptoms, the extent and location of the disease and whether there is a desire for pregnancy, patient age, adverse events, surgical complication rates and cost.
• Endogenous progesterone is secreted by the corpus luteum of the ovary, placenta and adrenal cortex. Progesterone prepares the inner lining of the uterus for pregnancy and maintains pregnancy by preventing ovulation during this time. The hormone increases basal body temperature, causes histologic changes in vaginal tissues, inhibits uterine contractions, inhibits pituitary secretion, stimulates mammary alveolar gland tissues and precipitates withdrawal bleeding in the presence of estrogen. The administration of progesterone to women with adequate estrogen production transforms the uterus from a proliferative phase to a secretory phase.
• The oral progestin agents are Food and Drug Administration (FDA) approved for a variety of clinical conditions. The FDA approved indications include the prevention of endometrial hyperplasia in postmenopausal women receiving conjugated estrogens (medroxyprogesterone, progesterone), palliative treatment of advanced breast and endometrium cancer (megestrol tablet), treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (medroxyprogesterone, norethindrone), treatment of human immunodeficiency virus (HIV)-related wasting (megestrol suspension), treatment of endometriosis (norethindrone), and treatment of secondary amenorrhea (medroxyprogesterone, norethindrone & progesterone).
The most common adverse reactions occurring during therapy with progesterone include menstrual irregularity, menstrual flow changes, dysmenorrhea or amenorrhea, weight gain, nausea/vomiting, mastalgia, dizziness, drowsiness and mild headache.

- **Black Box Warnings** (See Med Metrics Class review, Contraindications, pg. 25): Medroxyprogesterone and progesterone both have a black box warning that estrogens with progestins should not be used for the prevention of cardiovascular disease or dementia due to increased risks shown in The Women’s Health Initiative (WHI) estrogen plus progestin substudy. Additionally, the WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

- **Contraindications** (See MedMetrics Class Review, table 7, pg. 24):

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Medroxyprogestrone</th>
<th>Megestrol</th>
<th>Norethindrone</th>
<th>Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active arterial thromboembolic disease or history of these conditions</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Active deep vein thrombosis, pulmonary embolism, or history of these conditions</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Known or suspected estrogen-dependent neoplasia</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Known, suspected, or history of breast cancer</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Undiagnosed abnormal genital bleeding</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- **Precautions** (See MedMetrics Class Review, Table 8, pg. 26):

<table>
<thead>
<tr>
<th>Warning/Precaution</th>
<th>Medroxyprogestrone</th>
<th>Megestrol</th>
<th>Norethindrone</th>
<th>Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency; clinical cases have been observed in patients receiving or being withdrawn from chronic therapy in the stressed and non-stressed state</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Data suggest that progestin therapy may have adverse effects on lipid and carbohydrate metabolism; women with hyperlipidemias and/or diabetes should be monitored closely during progestin therapy</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Exacerbations of other conditions; estrogen plus progestin therapy may cause an exacerbation of asthma.</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**Warning/Precaution**

<table>
<thead>
<tr>
<th></th>
<th>Medroxyprogesterone</th>
<th>Megestrol</th>
<th>Norethindrone</th>
<th>Progestosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in patients with these conditions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluid retention; progestins may cause some degree of fluid retention</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>History of clinical depression; patients should be carefully observed and the drug discontinued if the depression recurs to a serious degree</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Peanut oil; product contains product oil and should not be used in patients allergic to peanuts</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>

- **Significant Drug-Drug Interactions:**
  - **medroxyprogesterone & norethindrone:**
    - **bosentan:** the efficacy of progestins may be reduced.
    - **rifamycins:** rifamycins may increase the elimination rate of progestins.
  - **levonorgestrel:**
    - **barbiturates:** both barbiturate induction of progestin metabolism and sex hormone-binding globulin synthesis may reduce progestin concentrations.
    - **hydantoins:** both hydantoins induction of progestin metabolism and sex hormone-binding globulin synthesis may reduce progestin concentrations.

- Head-to-head trials evaluating the progestins are limited. However, a trial that compared medroxyprogesterone, lynestrenol (not included in this review) and norethindrone for the treatment of endometrial hyperplasia did not show differences in the effectiveness.

  - **Primary endpoint:** After the cyclic progestin treatment for three months, none of the cases progressed. Patients receiving MPA showed resolution in 36.7% of the cases vs. 37.0% with patients receiving norethindrone. The highest rate of resolution was achieved with lynestrenol (56%), although there were no significant differences between the three treatments regarding the rate of women requiring further treatment for three months ($P=0.271$).
  - **At six month follow-up,** no endometrial curettages were needed. In patients ≤45 years of age, the resolution rates were 41.2, 42.9, and 43.8% with MPA, lynestrenol, and norethindrone, respectively. Corresponding values in patients >45 years of age were 30.8, 61.1, and 27.3%. There were no significant differences between treatments regarding resolution rates with respect to age (≤45 years; $P=0.989$ and >45 years; $P=0.113$).
  - **The use of megestrol 800mg/day suspension in patients ≥18 years of age for HIV related wasting demonstrates that compared to placebo, megestrol may increase food intake, improve appetite, increase body weight and improve sense of well-being.**
The daily caloric intake at weeks four and eight relative to baseline was greater in patients receiving megestrol compared to patients receiving placebo. By week 12, patients receiving placebo decreased their daily caloric intake by 241 calories from baseline, compared to patients receiving megestrol who increased their intake by 447 calories (difference, 688 calories; 95% CI; -144 to 1,521).

Body weight change from baseline at week twelve increased with megestrol 4.16 kg and decreased with placebo 0.61 kg (difference, 4.77 kg; 95% CI, 2.06 to 7.48).

Lastly, patients receiving megestrol had more positive answers to the well-being questionnaire compared to patients receiving placebo at weeks 4, 8, and 12.

The American Society for Reproductive Medicine guidelines state oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists, and anti-progestogens have all been utilized as medical treatments for endometriosis. There is no substantial evidence to support the superiority of one medical treatment over another; therefore, treatment decisions require individualization.

The use of hormonal therapy with estrogens and progestins for the treatment of moderate to severe vasomotor symptoms and other symptoms associated with menopause is well established and supported by current treatment guidelines. Specifically, progestins play an important role in preventing endometrial hyperplasia in postmenopausal women receiving estrogen therapy. However, long-term use of unopposed estrogen therapy or estrogen monotherapy is associated with an increased risk of endometrial hyperplasia and/or carcinoma. Nonetheless, addition of a progestin substantially reduces this risk.

The 2011 American Association of Clinical Endocrinologists (AACE) guidelines for treatment of menopause state unopposed estrogen should not be used in women with intact uterus and recommend progestin agents for a minimum of 10-14 days per month in women treated with estrogen who have an intact uterus.

The National Comprehensive Cancer Network Drugs & Biologics Compendium guidelines recommend megestrol as first line for invasive breast cancer in which the patient has not received prior endocrine therapy within one year or second line therapy (if patient has had prior endocrine therapy within one year or progression on another endocrine agent) for postmenopausal women or for premenopausal women treated with ovarian ablation/suppression who have recurrent or metastatic disease characterized by tumors that are estrogen-receptor and/or progestin-receptor positive.

RECOMMENDATION
The oral progestin agents are Food and Drug Administration (FDA) approved for a variety of clinical conditions. The FDA approved indications include prevention of endometrial hyperplasia in postmenopausal women receiving conjugated estrogens (medroxyprogesterone, progesterone), palliative treatment of advanced breast and endometrium cancer (megestrol tablet), treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (medroxyprogesterone, norethindrone), treatment of human immunodeficiency virus (HIV)-related wasting (megestrol suspension), treatment of endometriosis (norethindrone), and treatment of secondary amenorrhea (medroxyprogesterone, norethindrone & progesterone). In general the benefits and efficacy of hormonal therapy for these indications are well established. The American Society for Reproductive Medicine guidelines state oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists, and anti-progestogens have all been utilized as medical treatments for endometriosis. However, there is no substantial evidence to support the superiority of one medical treatment over another and treatment decisions require individualization. Additionally, clinical trials do not differentiate between the agents within the class in regards to safety and efficacy. Therefore, it is recommended that at least megestrol plus 2 other agents be available.
COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: ORAL PROGESTINS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>medroxyprogesterone (compares to Provera®)</td>
<td>Aygestin® (norethindrone) CC</td>
</tr>
<tr>
<td>megestrol acetate (compares to Megace®) QL</td>
<td>Megace® (megestrol acetate) QL</td>
</tr>
<tr>
<td>Prometrium® (progesterone)</td>
<td>Megace ES® (megestrol acetate conc.) CC, QL</td>
</tr>
<tr>
<td>norethindrone (compares to Aygestin®) CC</td>
<td>progesterone (compares to Prometrium®)</td>
</tr>
<tr>
<td>Provera® (medroxyprogesterone)</td>
<td>Megace ES® (megestrol acetate conc.)</td>
</tr>
</tbody>
</table>

Quantity Limits

<table>
<thead>
<tr>
<th>progestin</th>
<th>limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>megestrol acetate</td>
<td>600mL/month</td>
</tr>
<tr>
<td>Megace®</td>
<td>600mL/month</td>
</tr>
<tr>
<td>Megace ES®</td>
<td>150mL/month</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Megace ES®

Will be approved for individuals meeting one of the following criteria:
- Inability to swallow the 10mL (400mg) or 20mL (800mg) dose
- Intolerance to the original formulation

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Aygestin® (norethindrone)

Will be approved for patients with a diagnosis of endometriosis

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References

RE-REVIEW: ORAL, TRANSDERMAL & VAGINAL ESTROGENS

BACKGROUND

- This class review includes oral, transdermal and vaginal estrogen agents. Estrogens are FDA (Food and Drug Administration) approved for the treatment of moderate to severe vasomotor symptoms, vulvar and vaginal atrophy (transdermal/transvaginal estradiol, CE [equine/synthetic], esterified estrogens, estropipate), palliative treatment of metastatic breast cancer and advanced prostate cancer (estradiol, CE [equine], esterified estrogens) as well as for the prevention of postmenopausal osteoporosis (transdermal estradiol, CE [equine]) or osteoporosis (estropipate). Estrogens may also be used in the treatment of a variety of other conditions associated with a deficiency of estrogenic hormones, including female hypogonadism, castration, and primary ovarian failure (transdermal estradiol, CE [equine], esterified estrogens, estropipate).

- Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. Estradiol is the principal intracellular human estrogen which is substantially more potent than its metabolites, estrone and estriol, at the receptor level. Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism.

- Common Adverse Reactions (See MedMetrics Class Review, Table 6, pg. 39): Some common and serious adverse reactions include edema, hypertension, MI, stroke, venous thromboembolism, dementia exacerbation, dizziness, epilepsy exacerbation, headache, irritability, mental depression, angioedema, rash, urticaria, vomiting, weight gain/loss, nausea, mastalgia, pancreatitis, abdominal cramps, bloating and cholestatic jaundice
  - Black Box Warnings: The estrogen agents carry black box warnings for the following:
    - **Endometrial cancer**: unopposed estrogen in women with an intact uterus is associated with an increased risk of endometrial cancer. The addition of a progestin to estrogen therapy may decrease the risk of endometrial hyperplasia, a precursor to endometrial cancer.
    - **Breast cancer**: based on data from the Women’s Health Initiative (WHI) studies, an increased risk of invasive breast cancer was observed in postmenopausal women using conjugated estrogens (CE) in combination with medroxyprogesterone acetate (MPA).
    - **Dementia**: estrogens with or without progestin should not be used to prevent dementia. In the Women’s Health Initiative Memory Study (WHIMS), an increased incidence of dementia was observed in women ≥65 years of age taking CE alone or in combination with MPA.
    - **Cardiovascular disease**: estrogens with or without progestin should not be used to prevent cardiovascular disease. Data from the Women’s Health Initiative (WHI) studies showed an increased risk of deep vein thrombosis (DVT) and stroke has been reported with CE and an increased risk of DVT, stroke, pulmonary emboli (PE) and myocardial
infarction (MI) has been reported with CE with MPA in postmenopausal women.

- **Risk vs. benefits:** estrogens with or without progestin should be used for the shortest duration possible at the lowest effective dose consistent with treatment goals. Data related to treatment risks from the Women’s Health Initiative (WHI) studies, evaluated oral CE 0.625 mg with or without MPA 2.5 mg relative to placebo in postmenopausal women. Other combinations and dosage forms of estrogens and progestins were not studied. Outcomes reported from clinical trials using CE with or without MPA should be assumed to be similar for other doses and other dosage forms of estrogens and progestins until comparable data becomes available.

- **Contraindications (See MedMetrics Class Review, Table 7, pg. 45):** a few contraindications as it relates to estrogens include undiagnosed abnormal vaginal bleeding, DVT or PE (current or history of), active or recent (within 1 year) arterial thromboembolic disease (i.e. stroke, MI), carcinoma of the breast (known, suspected or history of) except in appropriately selected patients being treated for metastatic disease, estrogen-dependent tumor, hepatic dysfunction or disease and pregnancy.

- **Precautions (See MedMetrics class review, Table 8, pg. 52):**
  - Estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism. Discontinuation of treatment should be considered if pancreatitis occurs.
  - Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, discontinue the drug and take appropriate measures to reduce the serum calcium level.
  - Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy.
  - Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears to be dose- and duration-dependent.
  - In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens.
  - Exercise cautions in patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy; and in the case of recurrence, discontinue medication. Estrogens may be poorly metabolized in impaired liver function; use with caution.

- **Significant Drug-Drug Interactions:**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Interacting Medication or Disease</th>
<th>Potential Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens (CE, esterified estrogens (EE), estradiol, estropipate)</td>
<td>Barbiturates</td>
<td>Coadministration may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile.</td>
</tr>
<tr>
<td>Estrogens (CE, EE, estradiol, estropipate)</td>
<td>Bosentan</td>
<td>Bosentan may impair the efficacy of estrogens.</td>
</tr>
<tr>
<td>Estrogens (CE, EE, estradiol, estropipate)</td>
<td>Corticosteroids</td>
<td>May result in an increase in the pharmacologic and toxicological effects of corticosteroids.</td>
</tr>
<tr>
<td>Estrogens (CE, EE, estradiol, estropipate)</td>
<td>Hydantoins</td>
<td>Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested, but not confirmed.</td>
</tr>
</tbody>
</table>
### Generic Name | Interacting Medication or Disease | Potential Result
--- | --- | ---
Estrogens (CE, EE, estradiol, estropipate) | Rifamycins | Rifamycins may impair the effectiveness of estrogens; menstrual disturbances have been noted.
Estrogens (CE, EE, estradiol, estropipate) | Thyroid hormones | Serum-free thyroxine concentration may be decreased, increasing serum thyrotropin concentration and the need for thyroid hormone.
Estrogens (CE, EE, estradiol, estropipate) | Topiramate | The efficacy of estrogens may be decreased.

- **Clinical Trials:** Head-to-head trials do not consistently show superiority of one formulation over the other for the management of menopause symptoms.
  - A meta-analysis evaluated the efficacy of oral CE (equine) vs. oral 17β-estradiol vs. transdermal 17β-estradiol in postmenopausal women with hot flashes. The meta-analysis included 32 trials with varying durations. The primary endpoint measured relief of hot flashes and adverse events.
    - Primary endpoint: the number of hot flashes per week was significantly reduced with all forms of estrogen compared to placebo. The mean change in the number of hot flashes per week with:
      - oral CE(equine) treatment group: -19.1 (95% CI, -33.0 to -5.1)
      - oral 17β-estradiol treatment group: -16.8 (95% CI, -23.4 to -10.2)
      - transdermal 17β-estradiol group: -22.4 (95% CI, -35.9 to -10.4)
    - There was no significant difference between the agents in treatment of menopausal hot flashes (no P values reported). The estrogen agents showed similar short-term adverse effects. Breast tenderness and atypical vaginal bleeding were the most frequently reported adverse effects.
- The 2011 American Association of Clinical Endocrinologists (AACE) guidelines for the treatment of menopause state:
  - Menopausal hormone therapy (HT) may be appropriate for relief of severe menopausal symptoms in select postmenopausal women on the basis of individually determined benefit vs. risk profile.
  - The administration of the transdermal route of estrogen should be considered in order to avoid the hepatic “first-pass effect,” which may theoretically reduce the risk of thromboembolic disease.
  - The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption.
- The North American Menopause Society 2008 position statement for the use of estrogen and progestin in postmenopausal women states:
  - Estrogen therapy, with or without a progesterone, is the most effective treatment for menopause-related vasomotor symptoms and their potential consequences.
  - Estrogen therapy is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy.
  - When HT is considered solely for urogenital atrophy, local vaginal estrogen therapy is generally recommended.
RECOMMENDATION
Estrogens are FDA (Food and Drug Administration) approved for the treatment of moderate to severe vasomotor symptoms due to menopause, vulvar and vaginal atrophy, palliative treatment of metastatic breast cancer and advanced prostate cancer, as well as for the prevention of postmenopausal osteoporosis. The North American Menopause Society recognizes estrogen therapy, with or without progesterone, as the most effective treatment for menopause-related vasomotor symptoms and clinical data supports the use of estrogen for the treatment of moderate to severe vasomotor symptoms associated with menopause. Furthermore, clinical guidelines do not prefer one estrogen agent over the other and stress that decisions should be made on an individual basis. However, the AACE (American Association of Clinical Endocrinologists) guidelines state transdermal estrogen products may be considered to avoid the hepatic “first-pass effect” of oral estrogen agents. The guidelines also support the use of vaginal estrogen agents when minimal systemic absorption is desired or when hormonal therapy is utilized primarily for urogenital atrophy. Therefore given that hormonal therapy should be determined on an individual basis, it is recommended that at least one oral, one transdermal and one vaginal product be available for use to allow product selection among the various formulations.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

RE-REVIEW: ORAL, TRANSDERMAL & VAGINAL ESTROGENS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora (estradiol TDS)</td>
<td>Elestrin (estradiol gel)</td>
</tr>
<tr>
<td>Cenestin (CE, synthetic A)</td>
<td>EnJuvi (CE, synthetic B)</td>
</tr>
<tr>
<td>Climara (estradiol TDS)</td>
<td>Estrace (estradiol vaginal cream)</td>
</tr>
<tr>
<td>Divigel (estradiol gel)</td>
<td>Estraderm (estradiol TDS)</td>
</tr>
<tr>
<td>estradiol</td>
<td>estradiol TDS (compares to Climara®)</td>
</tr>
<tr>
<td>Estrin (estradiol vaginal)</td>
<td>Estrasorb (estradiol emulsion)</td>
</tr>
<tr>
<td>estropipate</td>
<td>Evamist (estradiol spray)</td>
</tr>
<tr>
<td>Premarin (CE, equine)</td>
<td>Femring (estradiol acetate vaginal)</td>
</tr>
<tr>
<td>Premarin Vaginal Cream (CE, equine vaginal)</td>
<td>Femtrace (estradiol acetate)</td>
</tr>
<tr>
<td>Vagifem (estradiol vaginal tab)</td>
<td>Menest (esterified estrogen)</td>
</tr>
<tr>
<td>Vivelle-Dot (estradiol TDS)</td>
<td>Menostar (estradiol TDS)</td>
</tr>
</tbody>
</table>

Quantity Limits

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora®</td>
<td>8/month</td>
</tr>
<tr>
<td>Climara®</td>
<td>4/month</td>
</tr>
<tr>
<td>estradiol TDS</td>
<td>4/month</td>
</tr>
<tr>
<td>Estraderm®</td>
<td>8/month</td>
</tr>
<tr>
<td>Menostar®</td>
<td>4/month</td>
</tr>
<tr>
<td>Premarin Vaginal Cream®</td>
<td>3/month</td>
</tr>
<tr>
<td>Vivelle-Dot®</td>
<td>8/month</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

References

RE-REVIEW: ORAL & TRANSDERMAL ESTROGENS/PROGESTINS

BACKGROUND

- Hormone replacement or estrogen/progesterone therapy (EPT) may be administered as estrogen monotherapy (in women without a uterus) or as combination therapy with an estrogen plus a progestin (in women with a uterus); addition of progestin reduces the risk of endometrial carcinoma in women with a uterus, but increases the risk of breast cancer.
- Although there are potential risks associated with the use of ET and EPT for the prevention of chronic diseases in postmenopausal women, the long-term safety of short-term hormone therapy for the management of menopausal symptoms is well established. Therefore, the decision between use of ET or EPT for the management of menopausal symptoms should be individualized and based on patient preference, chronic comorbidities, and the presence and severity of menopausal symptoms.
- Estrogen and progesterone also known as steroid hormones act by binding to their corresponding receptors on the female reproductive tract, the mammary gland, the hypothalamus, and the pituitary. Estrogens increase cervical secretions, cause proliferation of the endometrium, increase uterine tone, and prevent postmenopausal osteoporosis. Progestins reduce endometrial growth and risk of endometrial cancer by converting the endometrium from a proliferative to secretory phase.
- **FDA-Approved Indications:** This class review will include both oral and transdermal estrogen/progestin agents.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Prevention of Post-menopausal Osteoporosis</th>
<th>Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure</th>
<th>Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause</th>
<th>Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol/ drosiprenone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol/ levonorgestrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol/ norethindrone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol/ norgestimate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen, conjugated (CE) equine/ medroxy-progesterone (MPA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol/ norethindrone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Common and Severe Adverse Reactions** (See MedMetrics Class Review, Table 6, pg. 24): Some common and severe adverse reactions include headaches/migraines, mental depression, dizziness, fatigue or asthenia, nervousness, insomnia, diarrhea, dyspepsia,
vomiting and abdominal cramps/bloating, bleeding/spotting between menstrual periods, mastalgia, jaundice and pancreatitis.

- **Black Boxed Warning (See MedMetrics Class Review, pg. 27):** The estrogen/progesterone agents have a black box warning that estrogens with progestins should not be used for the prevention of cardiovascular disease or dementia due to increased risks shown in The Women's Health Initiative (WHI) estrogen plus progestin substudy. Additionally, the WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer as well. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

  - **Risk vs. benefits:** Estrogens with or without progestin should be used for the shortest duration possible at the lowest effective dose consistent with treatment goals. Data related to treatment risks from the Women’s Health Initiative (WHI) studies, evaluated oral CE 0.625 mg with or without MPA 2.5 mg relative to placebo in postmenopausal women. Other combinations and dosage forms of estrogens and progestins were not studied. Outcomes reported from clinical trials using CE with or without MPA should be assumed to be similar for other doses and other dosage forms of estrogens and progestins until comparable data becomes available.

- **Contraindications (See MedMetrics Class Review, Table 7, pg. 26):** A few contraindications include angioedema or anaphylactic reaction to estrogens or any component of the formulation, undiagnosed abnormal vaginal bleeding, DVT (deep vein thrombosis) or PE (pulmonary embolism) [current or history of], active or history of arterial thromboembolic disease (i.e. stroke, MI), carcinoma of the breast (known, suspected or history of), estrogen-dependent tumor, hepatic dysfunction or disease, known protein C, protein S and/or antithrombin deficiency or other known thrombophilic disorders and pregnancy.

- **Precautions (See MedMetrics Class Review, Table 8, pg. 29):**
  - Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism. If pancreatitis occurs, discontinuation of the drug is recommended.
  - Other medical conditions may be exacerbated by the use of EPT such as asthma and epilepsy.
  - Estrogen is poorly metabolized in patients with hepatic dysfunction. Use caution in patients with a history of cholestatic jaundice associated with prior estrogen use or pregnancy. Discontinue if jaundice develops or if acute or chronic hepatic disturbances occur. Use is contraindicated in patients with hepatic disease.

- **Significant Drug-Drug Interactions:**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Interacting Medication or Disease</th>
<th>Potential Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens (conjugated estrogens [CE], estradiol, ethinyl estradiol)</td>
<td>Barbiturates</td>
<td>Induction of hepatic microsomal enzymes by barbiturates increases the elimination of estrogenic substances, decreasing plasma concentration.</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol, ethinyl estradiol)</td>
<td>Bosentan</td>
<td>Bosentan may impair the efficacy of estrogens.</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol, ethinyl estradiol)</td>
<td>Corticosteroids</td>
<td>May result in an increase in the pharmacologic and toxicological effects of corticosteroids.</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Interacting Medication or Disease</td>
<td>Potential Result</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol, ethinyl estradiol)</td>
<td>Rifamycins</td>
<td>Rifamycins may impair the effectiveness of estrogens; menstrual disturbances have been noted.</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol, ethinyl estradiol)</td>
<td>Thyroid hormones</td>
<td>Serum-free thyroxine concentration may be decreased, increasing serum thyrotropin concentration and the need for thyroid hormone.</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol, ethinyl estradiol)</td>
<td>Topiramate</td>
<td>The efficacy of estrogens may be decreased.</td>
</tr>
<tr>
<td>Estrogens (CE, estradiol)</td>
<td>Hydantoins</td>
<td>Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested, but not confirmed.</td>
</tr>
<tr>
<td>Progestins (MPA, norethindrone)</td>
<td>Bosentan</td>
<td>The efficacy of progestins may be reduced.</td>
</tr>
<tr>
<td>Progestins (MPA, norethindrone)</td>
<td>Rifamycins</td>
<td>Rifamycins may increase the elimination rate of progestins.</td>
</tr>
<tr>
<td>Progestins (levonorgestrel)</td>
<td>Barbiturates</td>
<td>Both barbiturate induction of progestin metabolism and sex hormone-binding globulin synthesis may reduce progestin concentrations.</td>
</tr>
<tr>
<td>Progestins (levonorgestrel)</td>
<td>Hydantoins</td>
<td>Both hydantoin induction of progestin metabolism and sex hormone-binding globulin synthesis may reduce progestin concentrations.</td>
</tr>
<tr>
<td>Progestins (MPA)</td>
<td>Aminoglutethimide</td>
<td>Aminoglutethimide may decrease medroxyprogesterone serum concentrations and perhaps its effectiveness.</td>
</tr>
</tbody>
</table>

- **Clinical Trials:** Both oral and transdermal estrogen/progestin agents have demonstrated effectiveness for the treatment of symptoms associated with menopause. Head-to-head trials within the class are limited. In one head-to-head trial comparing estrogen, conjugated equine/medroxyprogesterone acetate and estradiol/norethindrone in healthy postmenopausal women, the study showed a significantly larger proportion of patients receiving estradiol/norethindrone reported no bleeding and spotting.

- **The 2011 American Association of Clinical Endocrinologists (AACE) guidelines for the treatment of menopause state:**
  - Menopausal hormone therapy (HT) may be appropriate for relief of severe menopausal symptoms in select postmenopausal women on the basis of individually determined benefit vs. risk profile.
  - The administration of the transdermal route of estrogen should be considered in order to avoid the hepatic “first-pass effect,” which may theoretically reduce the risk of thromboembolic disease.
  - The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption.

- **The North American Menopause Society 2008 position statement for the use of estrogen and progestin in postmenopausal women states:**
  - Estrogen therapy, with or without a progesterone, is the most effective treatment for menopause-related vasomotor symptoms and their potential consequences.
  - Estrogen therapy is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy.
  - When HT is considered solely for urogenital atrophy, local vaginal estrogen therapy is generally recommended.
RECOMMENDATION

The oral and transdermal estrogen/progestin agents are Food and Drug Administration (FDA)-approved for the prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause and treatment of moderate to severe vasomotor symptoms due to menopause. Specifically, transdermal estradiol/norethindrone is the only agent in the class that is FDA-approved for the treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Current clinical guidelines support the use of estrogen and progestins for the treatment of moderate to severe vasomotor symptoms and other symptoms associated with menopause; stating it is the most effective treatment for vasomotor symptoms. However, due to potential risks associated with EPT, the decision to use EPT for management of menopausal symptoms should be assessed on an individual basis. Although guidelines do not prefer one estrogen/progestin agent over another, the AACE (American Association of Clinical Endocrinologists) guidelines state transdermal hormonal preparations may be considered to avoid the hepatic first-pass effect of oral preparations. Therefore it is recommended that at least two oral estrogen/progestin agents be available for use. Additionally, to allow for treatment of estrogen deficiency secondary to other conditions, at least one transdermal estrogen/progestin agent should also be available.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

RE-REVIEW: ORAL & TRANSDERMAL ESTROGENS/PROGESTINS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activella® (estradiol/norethindrone)</td>
<td>Angeliq® (estradiol/drospirenone)</td>
</tr>
<tr>
<td>Combipatch® (estradiol/norethindrone)</td>
<td>Climara Pro® (estradiol/levonorgestrel)</td>
</tr>
<tr>
<td>Femhrt® low dose</td>
<td>estradiol/norethindrone (compares to Activella®)</td>
</tr>
<tr>
<td>Jevantique™ (ethinyl estradiol/norethindrone)</td>
<td>FemHRT® 1/5 (ethinyl estradiol/norethindrone)</td>
</tr>
<tr>
<td>PreFest® (estradiol/norgestimate)</td>
<td>Jintel™ (ethinyl estradiol/norethindrone)</td>
</tr>
<tr>
<td>PremPhase® (Conjugated estrogen/MPA)</td>
<td>Mimvey™ (estradiol/norethindrone)</td>
</tr>
<tr>
<td>PremPro® (Conjugated estrogen/MPA)</td>
<td></td>
</tr>
</tbody>
</table>

Quantity Limits

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Climara Pro®</td>
<td>4/month</td>
</tr>
<tr>
<td>CombiPatch®</td>
<td>8/month</td>
</tr>
<tr>
<td>PremPhase®</td>
<td>28 tablets/month</td>
</tr>
<tr>
<td>PremPro®</td>
<td>28 tablets/month</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

References

6. No authors listed. Estrogen and progestogen use in postmenopausal women: 2010
RE-REVIEW: LUTEINIZING HORMONE-RELEASING HORMONE AGENTS

BACKGROUND

- Endometriosis is a common, benign and estrogen-dependent condition. Some patients with endometriosis may not experience symptoms while others may experience distressing and debilitating symptoms such as pelvic pain, severe dysmenorrhea, dyspareunia and infertility. Surgical and medical treatments are available for the management of endometriosis. According to the American Society for Reproductive Medicine, oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists (GnRH) and anti-progestogens have all been utilized as medical treatments for endometriosis. However, there is no high quality evidence to support the superiority of one medical treatment over another. Therefore, treatment decisions are individualized. Decisions are based on the severity of symptoms, the extent and location of the disease and whether there is a desire for pregnancy, patient age, adverse events, surgical complication rates and cost.

- Central Precocious Puberty (CPP) also referred to as “precocious puberty” is defined as the early onset of puberty before age eight in girls and age nine in boys. There are 3 classifications of precocious puberty, based on the underlying pathologic process. The first, gonadotropin-dependent precocious puberty, is caused by early maturation of the entire hypothalamic-pituitary-gonadal (HPG) axis, with the full spectrum of physical and hormonal changes of puberty. Gonadotropin-independent is another form caused by excessive secretion of sex hormones derived from the gonads or adrenal glands. This form may or may not be appropriate for the child’s gender, with virilization of girls and feminization of boys. The third form is known as incomplete precocious puberty, characterized by either early breast development in girls or isolated male hormone-mediated sexual characteristics (i.e. pubic/axillary hair, acne) with no other signs of puberty or advanced growth. GnRH analogs are used as the primary treatment for gonadotropin-independent precocious puberty. Use of GnRH agonists in gonadotropin-independent precocious puberty is not effective. Therefore, treatment of gonadotropin-independent precocious puberty should be directed at the underlying pathology. In these patients, surgery; a combination of surgery, radiation therapy, and chemotherapy; glucocorticoid therapy and removal of exogenous estrogen exposure may be appropriate treatment options. Patients with incomplete precocious puberty do not require therapy. However these patients should be re-examined regularly.

- This class review includes the luteinizing hormone-releasing hormone agent (or GnRH agonist, nafarelin acetate (Synarel®)). Nafarelin acetate is a potent synthetic agonist analog of naturally occurring GnRH that enhances the release of pituitary gonadotropins luteinizing hormone and follicle-stimulating hormone. The actions of nafarelin acetate result in a temporary rise of gonadal steroidogenesis. However, repeated administration of the agent suppresses the stimulatory effect on the pituitary gland.

- Nafarelin acetate is FDA (Food and Drug Administration) approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions, as well as for the treatment of central precocious puberty in children of both sexes.

- Common Adverse Reactions (See MedMetrics class review, Tables 6 & 7, pg. 10): Some common and adverse reactions include acne, headache, hot flashes, transient breast enlargement, vaginal bleeding, emotional lability, transient increase in pubic hair, body odor, seborrhea and decreases in serum calcium and white blood cell counts.
  
  o Nafarelin is contraindicated in women with undiagnosed abnormal vaginal bleeding. This agent is also contraindicated in pregnancy (FDA pregnancy risk
category X) or in females who may become pregnant. Pregnancy should be excluded before starting treatment with nafarelin.

- The diagnosis of central precocious puberty (CPP) must be established before treatment with nafarelin acetate is initiated. Regular monitoring of CPP patients is needed to assess both patient response and compliance, especially during the first 6—8 weeks of therapy to ensure the that suppression of pituitary gonadal function is rapid.
- There are no clinically significant drug interactions associated with nafarelin.

- There are a limited number of clinical trials which evaluate nafarelin acetate for the treatment of precocious puberty. However, in the management of endometriosis, clinical trials consistently demonstrate effectiveness of nafarelin acetate in regards to laparoscopic scores and pain-related symptoms.
  - A double-blind, randomized controlled trial evaluated nafarelin nasal spray versus treatment with danazol for 180 days. This trial included 59 patients and showed both treatments resolved pelvic tenderness, induration, pelvic pain, dysmenorrhea, and dyspareunia. There were no significant differences were noted in efficacy endpoints between the two treatments with regards to laparoscopic and total symptom severity scores at 90 and 180 days (P values not reported). Also, no significant differences were noted between the two treatments with regards to overall incidences of adverse events.

- The American Society for Reproductive Medicine guidelines for treatment of pain associated with endometriosis states:
  - Both medical and surgical treatments for endometriosis are effective.
  - Oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone (GnRH) agonists, and anti-progestogens all have been employed for the treatment of endometriosis.
  - No clinical trials have compared directly medical versus surgical treatment of endometriosis; therefore, there is no substantial evidence to establish the superiority of one approach over the other.

**RECOMMENDATION**

Nafarelin acetate is FDA (Food and Drug Administration) approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Clinical guidelines indicate both surgical and medical treatments are effective for endometriosis and do not establish one treatment option over the other. The American Society for Reproductive Medicine guidelines list gonadotropin-releasing hormone agonist as a drug option along with other agents for the treatment of endometriosis. Additionally, nafarelin acetate is FDA approved for the treatment of central precocious puberty in children of both sexes. Therefore it is recommended that nafarelin acetate be available for use.

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>RE-REVIEW: LUTEINIZING HORMONE-RELEASING HORMONE AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>Synarel® (nafarelin acetate)</td>
</tr>
<tr>
<td><strong>NON-PREFERRED</strong></td>
</tr>
</tbody>
</table>

**References**

4. No authors listed. Treatment of pelvic pain associated with endometriosis. Practice Committee of
BACKGROUND

- Adrenocorticotropic hormone (ACTH), a key element of the hypothalamic-pituitary-adrenal (HPA) axis, is secreted by the anterior pituitary gland upon stimulation from corticotropin-releasing hormone. ACTH acts on the adrenal cortex to stimulate the secretion of cortisol, which then suppresses the release of corticotropin-releasing hormone from the hypothalamus in a negative feedback pathway. H.P. Acthar® Gel (corticotropin) is a highly purified, natural porcine ACTH that is formulated as a repository gel for prolonged release after intramuscular or subcutaneous injection.
- The mechanism of action of ACTH in infantile spasms is unknown; however, it is hypothesized to be due to the suppression of corticotropin-releasing hormone, which may play a role in provoking seizure activities.
- Corticotropin is FDA-approved for the treatment of infantile spasms in addition to a variety of glucocorticoid-responsive, nonendocrine disorders, including acute exacerbations of multiple sclerosis, rheumatic disorders, nephrotic syndrome and inflammatory ophthalmic diseases.
- The adverse effects of ACTH are related primarily to its steroidogenic effects with the most common adverse events including acne, diarrhea, hypertension, infection and irritability. Serious adverse events include cardiomegaly, Cushing’s syndrome, seizures and encephalitis.
  - The use of ACTH is contraindicated in infants with suspected congenital infections and in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency or adrenocortical hyperfunction. Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of ACTH. In addition, corticotropin is contraindicated for intravenous administration and in patients with sensitivity to porcine proteins.
  - ACTH may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Hypothalamic-pituitary-adrenal axis suppression may occur following prolonged ACTH therapy with the potential for adrenal insufficiency after withdrawal of the medication. Signs and symptoms of Cushing’s syndrome may occur during treatment with ACTH but generally resolve after therapy is discontinued.
  - ACTH may cause blood pressure elevation, salt and water retention, increased excretion of potassium and calcium, gastrointestinal bleeding and gastric ulcer. Use of ACTH may be associated with central nervous system effects such as euphoria, insomnia, irritability, mood swings, personality changes, severe depression and psychotic manifestations. Treatment may also aggravate existing emotional instability or psychotic tendencies. Prolonged use of ACTH may lead to posterior subcapsular cataracts, glaucoma with damage to the optic nerves and may increase the risk of secondary ocular infections due to fungi and viruses. Patients may develop antibodies to ACTH after chronic administration and loss of endogenous and exogenous ACTH activity. Prolonged use may also have negative effects on growth and physical development in children. Changes in appetite are associated with ACTH and are reversible once therapy is stopped. Treatment is associated with decreases in bone formation, an increase in bone resorption and inhibition of osteoblast function, which may lead to inhibition of
bone growth in children and adolescents and development of osteoporosis at any age.

- **Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Interacting Medication or Disease</th>
<th>Potential Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin</td>
<td>Anticholinesterases</td>
<td>Corticotropin may decrease the effect of anticholinesterases. Monitor the clinical efficacy of anticholinesterases.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Anticoagulants</td>
<td>Corticotropin may alter the hypoprothrombinemic effect of anticoagulants. Monitor and adjust the anticoagulant doses as needed.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Carbamazepine</td>
<td>Carbamazepine may reduce the effect of corticotropin. Higher doses of corticotropin may be required.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Diuretics</td>
<td>Corticotropin may potentiate electrolyte loss associated with diuretic therapy. Monitor electrolytes and supplement as needed.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Fluoroquinolones</td>
<td>Corticotropin may increase the risk of tendon rupture associated with fluoroquinolone therapy. Monitor for tendon- and joint-related adverse effects.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Interleukin-2</td>
<td>Corticotropin may decrease the effect of interleukin-2. The use of these agents in combination should be avoided.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Itraconazole</td>
<td>Itraconazole may increase the serum concentration of corticotropin. Monitor for corticotropin adverse effects.</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Mifepristone</td>
<td>Mifepristone may increase the serum concentration of corticotropin. The use of these agents in combination is contraindicated.</td>
</tr>
</tbody>
</table>

- The efficacy of ACTH in the treatment of infantile spasms is well-established. Results from a meta-analysis of 14 randomized controlled trials comparing the efficacy of treatment options for infantile spasms showed that hormonal treatments (i.e., ACTH, tetracosactide and high-dose prednisolone) achieved a higher rate of cessation of spasms compared to vigabatrin in patients with infantile spasms.
  - Vigabatrin had a lower cessation rate compared to hormonal treatment, including ACTH, tetracosactide and high-dose prednisolone (OR, 0.42; 95% CI, 0.21 to 0.80). Time to achieve cessation was one to 14 days with vigabatrin and two to 12 days with ACTH.

- The Infantile Spasms Working Group released a Consensus Report in 2010 which stated that ACTH is considered first-line therapy for infantile spasms; however, this consensus report also stated that vigabatrin is considered first-line therapy for infantile spasms and made no distinction between the two agents. The American Academy of Neurology (AAN) recently released an evidence-based guideline update on the medical treatment of infantile spasms. The Academy concluded that ACTH is more effective than vigabatrin for short-term treatment of children with infantile spasms (excluding those with tuberous sclerosis complex). The AAN recommends that ACTH or vigabatrin may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over vigabatrin. Corticotropin is also FDA-approved for the treatment of a variety of glucocorticoid-responsive, nonendocrine disorders, including acute exacerbations of multiple sclerosis, rheumatic disorders, nephrotic syndrome and inflammatory ophthalmic diseases. The consensus guidelines for these indications generally recommend the use of an intravenous or oral glucocorticoid when systemic glucocorticoid therapy is warranted.
RECOMMENDATION
Corticotropin, a natural porcine ACTH, is FDA approved for the treatment of infantile spasms as well as a variety of glucocorticoid-responsive disorders. Current clinical guidelines recommend ACTH as first-line therapy for the treatment of infantile spasms. For all other FDA-approved indications, consensus guidelines generally recommend the use of intravenous or oral glucocorticoids when glucocorticoid therapy is warranted. Therefore, it is recommended corticotropin should be available for use in the treatment of infantile spasms and should be subject to step therapy for all other indications.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: HORMONES: ADRENOCORTICOTROPIC

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>H.P. Acthar®</td>
</tr>
</tbody>
</table>

Quantity Limits:
H.P. Acthar®  1 mL/day

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for H.P. Acthar®
Corticotropin will be approved only for recipients who are self-administering and meet ONE of the following criteria:
- Difficulty swallowing or inability to absorb oral medications
- Contraindication or intolerance to oral AND injectable glucocorticoids
- Diagnosis of infantile spasms

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References
BACKGROUND

- Hypothyroidism is a condition resulting from undersecretion of thyroid hormone from the thyroid gland. In the United States the most common cause of primary hypothyroidism is Hashimoto’s disease. Causes of secondary hypothyroidism include pituitary and hypothalamic disease. For the majority of patients with hypothyroidism treatment with thyroid hormone replacement therapy will be lifelong. The goal of such therapy is restoration of the euthyroid state. Appropriate treatment reverses all of the clinical manifestations of hypothyroidism. Thyroid agents contain either thyroxine (T4) (levothyroxine), triiodothyronine (T3) (liothyronine), a combination of T3 and T4 (liotrix), or desiccated mixtures of T3 and T4 (thyroid).
- The levothyroxine agents (Levothroid®, Levoxyl®, Synthroid®, Tirosint® and Unithroid®); liothyronine agent (Cytomel®); liotrix (T3-T4) agent (Thyrolar®) and thyroid agent (Armour Thyroid® and NP Thyroid®) are all indicated for the management of hypothyroidism and utilized as thyroid hormone replacement therapy in this clinical setting.
- Adverse events, other than those indicative of hyperthyroidism because of therapeutic overdosage, are rare with the thyroid agents.
  - All of the thyroid agents are associated with a Black Box Warning recommending against the use of these agents for the treatment of obesity or for weight loss. Use of thyroid agents in this setting is unjustified and has shown to be ineffective.
  - All of the thyroid agents are contraindicated in uncorrected adrenal insufficiency and in untreated subclinical or overt thyrotoxicosis of any etiology. Additionally, levothyroxine is contraindicated in patients with acute myocardial infarction.

<table>
<thead>
<tr>
<th>Warning/Precaution</th>
<th>Levothyroxine</th>
<th>Liothyronine</th>
<th>Liotrix</th>
<th>Thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune polyglandular syndrome; chronic autoimmune thyroiditis may occur in association with other autoimmune disorders</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular disease; use with great caution</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Concomitant diabetes or adrenal cortical insufficiency; thyroid hormone therapy aggravates the intensity of symptoms</td>
<td>-</td>
<td>-</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Decreases in bone mineral densities have been associated with long-term treatment in women</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperthyroidism increases sensitivity to oral anticoagulants; prothrombin time should be closely monitored in thyroid patients on oral anticoagulants</td>
<td>-</td>
<td>-</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Hypothalamic/pituitary hormone deficiencies; in patients with secondary or tertiary hypothyroidism, consider and, if diagnosed, treat additional hypothalamic/pituitary hormone deficiencies</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infants with congenital hypothyroidism; increased risk for other congenital anomalies</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infertility; do not use to treat male or female infertility unless this condition is associated with hypothyroidism</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphologic hypogonadism and</td>
<td>-</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Warning/Precaution | Levothyroxine | Liothyronine | Liotrix | Thyroid
--- | --- | --- | --- | ---
nephrosis; rule out before treatment initiation |  |  |  | 
Narrow therapeutic index; careful dosage titration is necessary | ✓ | - | - | -
Severe and prolonged hypothyroidism can lead to a decreased level of adrenocortical activity commensurate with the lowered metabolic state | - | ✓ | - | -
Use of thyroid hormones in the therapy of obesity, alone or combined with other drugs is unjustified and has been shown to be ineffective | ✓ | ✓ | ✓ | ✓

- Levothyroxine should be taken at least four hours apart from drugs known to interfere with its absorption, including cholestyramine, colesevelam, sucralfate, antacids and iron salts.

- Clinical trial data consistently demonstrate that thyroid hormone levels are normalized with individualized doses of thyroid hormone, and improvements in quality of life and cognitive function tests are observed as well. Several clinical trials have compared T4 monotherapy and combination treatment with T3 and T4. Overall, the majority of data does not support the use of combination treatment over T4 monotherapy. While both treatments are effective, combination therapy does not achieve further clinical benefits in normalizing thyroid hormone levels or in improving quality of life, cognitive function, or other biochemical markers compared to monotherapy with T4.

- Current guidelines from the American Association of Clinical Endocrinologists (AACE) state that clinical hypothyroidism should be treated with levothyroxine replacement therapy and that in general, desiccated thyroid hormone, combinations of thyroid hormones, or triiodothyronine should not be used as replacement therapy. The AACE advocates the use of high-quality brand preparation T4. Furthermore, they state bioequivalence of T4 preparations is based on total T4 measurement and not thyroid-stimulating hormone levels; therefore, bioequivalence is not the same as therapeutic equivalence. In addition, various brands of T4 are not compared against a T4 standard. According to the AACE, it is preferred for patients to receive the same brand of T4 throughout treatment. 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.

### RECOMMENDATION
Thyroid hormone replacement therapy with the thyroid agents is the mainstay of treatment for patients with hypothyroidism, and will be administered lifelong for the majority of patients. All of the thyroid hormones have similar FDA-approved indications and safety profiles. Current clinical guidelines state that levothyroxine is the treatment of choice for the management of hypothyroidism and that in general, desiccated thyroid hormone, combinations of thyroid hormones, or triiodothyronine should not be used as replacement therapy. Clinical trial data demonstrate that combination T3 and T4 treatment is not associated with consistent clinical benefits over monotherapy with levothyroxine. 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. Therefore, it is recommended at least levothyroxine and liothyronine should be available for use in patients with hypothyroidism.

### COMMITTEE VOTE:

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
</table>
RE-REVIEW: HORMONES: THYROID

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomel® (liothyronine)</td>
<td>Armour Thyroid® (thyroid)</td>
</tr>
<tr>
<td>Levothroid® (levothyroxine)</td>
<td>NP Thyroid® (compares to Armour Thyroid)</td>
</tr>
<tr>
<td>levothyroxine (compares to Synthroid®)</td>
<td>Thyrolar® (liotrix)</td>
</tr>
<tr>
<td>Levoxyl® (levothyroxine)</td>
<td>Tirosint® (levothyroxine)</td>
</tr>
<tr>
<td>liothyronine (compares to Cytomel®)</td>
<td></td>
</tr>
<tr>
<td>Synthyroid® (levothyroxine)</td>
<td></td>
</tr>
<tr>
<td>Unithroid® (levothyroxine)</td>
<td></td>
</tr>
<tr>
<td>Armour Thyroid® (thyroid)</td>
<td></td>
</tr>
<tr>
<td>NP Thyroid® (compares to Armour Thyroid)</td>
<td></td>
</tr>
<tr>
<td>Thyrolar® (liotrix)</td>
<td></td>
</tr>
<tr>
<td>Tirosint® (levothyroxine)</td>
<td></td>
</tr>
</tbody>
</table>

References


RE-REVIEW: HORMONES: ANTI-THYROID

BACKGROUND

- Hyperthyroidism is the consequence of excessive thyroid hormone action. There are several causes of hyperthyroidism, which include toxic diffuse goiter (Graves’ disease), toxic adenoma, toxic multinodular goiter (Plummer’s disease), painful subacute thyroiditis, silent thyroiditis, iodine-induced hyperthyroidism, excessive pituitary thyroid-stimulating hormone (TSH) or trophoblastic disease, and excessive ingestion of thyroid hormone. Included in this review are the anti-thyroid agents, methimazole and propylthiouracil.

- Both methimazole and propylthiouracil are indicated in patients with Graves’ disease with hyperthyroidism or toxic multinodular goiter for whom surgery or radioactive iodine therapy is not an appropriate treatment option and to ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy.

- The most common adverse effect with both methimazole and propylthiouracil is rash. Less common, but severe adverse effects with methimazole include agranulocytosis, aplastic anemia and hepatotoxicity. Less common, but severe adverse effects with propylthiouracil include hepatic necrosis, liver failure and nephritis.

- Propylthiouracil carries a black-box warning regarding the risk of severe liver injury and acute liver failure. Due to this risk, its use should be reserved for patients who cannot tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

- Both methimazole and propylthiouracil are associated with a risk of hepatic toxicity although the risk appears to be less with methimazole than with propylthiouracil, especially in pediatric patients. Both agents are pregnancy category D; however, methimazole readily crosses the placental membranes and can cause fetal harm, particularly when administered in the first trimester of pregnancy.
Serum levels of digitalis glycosides are increased in hypothyroidism or when hyperthyroid patients on a stable digitalis glycosides regimen are rendered euthyroid by anti-thyroid agents. The therapeutic effect of digitalis glycosides may be increased and toxicity may occur. Increases in theophylline clearance can be expected in hyperthyroid patients; however, clearance returns to normal when euthyroid state is achieved by administration of anti-thyroid agents. The action of warfarin may be changed during coadministration of anti-thyroid agents.

- Clinical trials evaluating varying dosages of methimazole and propylthiouracil demonstrate that while improvements in thyroid function tests and remission of hyperthyroidism are achievable with anti-thyroid agents, relapse and recurrence are common. Head-to-head trials demonstrate that both methimazole and propylthiouracil are effective treatments for Graves' disease, with no significant differences in efficacy observed between the two agents.

- Three types of therapy are available for Graves' disease: surgical intervention, anti-thyroid drugs, and radioactive iodine. Although thyroidectomy for Graves' disease was frequently used historically, it is now uncommon in the United States unless coexistent thyroid cancer is suspected. Current guidelines from the American Academy of Clinical Endocrinologists state that radioactive iodine is currently the treatment of choice for Graves' disease. Radioactive iodine therapy is contraindicated in pregnancy; therefore, use of the anti-thyroid agents is recommended in this setting, with propylthiouracil preferred over methimazole. In addition, anti-thyroid agents may be preferred over radioactive iodine therapy in children with Graves' disease. Elderly or cardiac patients with Graves' disease may require anti-thyroid agents before treatment with radioactive iodine to deplete the thyroid gland of stored hormone and reduce the risk of excessive post-treatment hyperthyroidism as a result of iodine-induced thyroiditis. Overall, treatment of Graves' disease with anti-thyroid agents alone is an alternative therapeutic strategy that is used in a minority of patients within the United States.

**RECOMMENDATION**

The anti-thyroid agents methimazole and propylthiouracil are indicated in patients with Graves' disease with hyperthyroidism or toxic multinodular goiter for whom surgery or radioactive iodine therapy is not an appropriate treatment option and to ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy. Within the United States radioactive iodine therapy is the treatment of choice for Graves' disease. Anti-thyroid agents are recommended over radioactive iodine therapy during pregnancy, and may be the preferred treatment strategy in children with Graves' disease. Due to reports of severe liver injury and acute liver failure, propylthiouracil should be reserved for patients who cannot tolerate methimazole. Conversely, because of the risk of fetal abnormalities associated with methimazole, propylthiouracil is the preferred anti-thyroid agents for use in pregnant women with hyperthyroidism. Although treatment of Graves' disease with anti-thyroid agents alone is an alternative therapeutic strategy that is used in a minority of patients within the United States, methimazole and propylthiouracil are the only available anti-thyroid agents with each agent preferred in a different population subset. Therefore, it is recommended both methimazole and propylthiouracil should be available for use.

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>RE-REVIEW: HORMONES: ANTI-THYROID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>methimazole (compares to Tapazole®)</td>
</tr>
</tbody>
</table>
References

# Clinical Criteria for Isonarif®, Rifamate® & Rifater®
- Recipient must be unable to take the components individually.

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

## Clinical Criteria for Dymista®
- Recipient must be unable to take the two components individually.

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

## Clinical Criteria for Horizant®
Horizant® will be approved for patients meeting the following criteria:
- Diagnosis of Restless Leg Syndrome, AND trial and failure, contraindication or intolerance to BOTH pramipexole AND ropinirole
- Diagnosis of post-herpetic neuralgia who have tried and failed gabapentin AND had a failure, contraindication or intolerance to ONE of the following:
  - A tricyclic antidepressant
  - An anticonvulsant (other than gabapentin)

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

## Clinical Criteria for Korlym®
Korlym will be approved for patients meeting ALL the following criteria:
- Diagnosis of Cushing’s Syndrome
- Type 2 diabetes mellitus or glucose intolerance
- Have failed surgical treatment OR are not candidate for surgery
Korlym will **NOT** be approved for use in pregnancy.

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

## Clinical Criteria for Leuprolide:
Leuprolide will be approved for patients meeting ONE of the following criteria:
- Diagnosis of prostate cancer in male patient
- Diagnosis of central precocious puberty in children

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

## Clinical Criteria for Eligard®:
Eligard® will be approved for patients meeting the following criteria:
- Diagnosis of prostate cancer in male patient
<table>
<thead>
<tr>
<th>COMMITTEE VOTE:</th>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Criteria for Lupron Depot®:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupron Depot® will be approved for patients meeting ONE of the following criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of prostate cancer in male patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of endometriosis in female patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of uterine leiomyomas in female patient</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMITTEE VOTE:</th>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Criteria for Lupron Depot-PED®:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupron Depot-PED® will be approved for patients meeting ONE of the following criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of central precocious puberty in children</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMITTEE VOTE:</th>
<th>APPROVED</th>
<th>DISAPPROVED</th>
<th>APPROVED with MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantity Limits:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilaudid®</td>
<td>8/day 300 mg/30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydromorphone</td>
<td>8/day 300 mg/30 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>