Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

February 17, 2011
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)

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¹ AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
RE-REVIEW: OPHTHALMIC IMMUNOMODULATORS

BACKGROUND

- Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation. Disease and dysfunction on the ocular surface results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface which plays a role in the pathogenesis of KCS. Symptoms of KCS include dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision. More severe complications include corneal scarring, ulceration or perforation. Ophthalmic cyclosporine is the only currently available ophthalmic immunomodulator.

- The exact mechanism of action for cyclosporine ophthalmic emulsion is unknown; however in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS, cyclosporine ophthalmic emulsion is thought to act as a partial immunomodulator.

- Cyclosporine ophthalmic emulsion is FDA approved to increase tear production in patients with KCS.

- The most common adverse effects of ophthalmic cyclosporine is ocular burning sensation, conjunctival hyperemia, pruritis, and blurring.
  - Cyclosporine ophthalmic emulsion is contraindicated in patients with active ocular infections.
  - Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; a fifteen minute interval should separate administration.
  - Due to the limited systemic absorption of cyclosporine ophthalmic emulsion, no drug interactions have been reported.

- At this time there are limited clinical trial data available to evaluate cyclosporine ophthalmic emulsion. FDA approval was based on two randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients. All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the two placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms.

- One additional trial compared cyclosporine to the use of punctal occlusion and the combination of both therapies; both groups were also allowed to use concomitant artificial tears throughout the study (n=30). Patients had moderate dry eye disease defined as chronic symptoms of burning and scratchiness in both eyes; daily need for multiple applications of artificial tears; and rose bengal staining of grade ≥2. The primary endpoints were Schirmer scores (without anesthesia), corneal and conjunctival rose bengal staining, and artificial tear use. The plug and combination groups demonstrated a significant improvement relative to baseline (P≤0.005) and cyclosporine (P<0.001) in mean Schirmer scores at the one and three month follow up visits. Initial response was not seen in the cyclosporine group; these patients achieved a significant improvement from baseline at the six month follow up visit (P≤0.005) which was indistinguishable from the other groups (P values not reported). Mean artificial tear use declined significantly from baseline in every treatment group at one and three months (P≤0.005 for all), except for the cyclosporine group at one month. By the end of the study, the cyclosporine group demonstrated a significant change from baseline in artificial tear use (P≤0.005) that was statistically indistinguishable from other treatment groups.

- Cyclosporine ophthalmic emulsion is utilized in the treatment of related ophthalmic disorders along with the dry eye condition associated with KCS. Dry eye can be stratified by severity level into three categories based on the signs and symptoms of disease, with treatment recommendations specific for disease severity.
Clinical guidelines from the American Academy of Ophthalmology (AAO) Practice Patterns for Dry Eye syndrome recommend a step therapy approach to treating dry eyes based on classifications of mild, moderate and severe disease as outlined below:

- Treatment of mild dry eyes should include environmental modifications, discontinuation of any offending topical or systemic medications, aqueous enhancement using artificial tear substitutes, gels or ointments, eye lid therapy (warm compressions and good hygiene) and treatment of other contributing ocular factors (blepharitis or meibomianitis).
- Treatment for moderate dry eyes should include treatments for mild dry eyes and then additive therapy with anti-inflammatory agents (topical corticosteroids, cyclosporine), systemic omega 3-fatty acid supplements, punctal plugs, spectacle side shields, or moisture chambers.
- Treatment for severe dry eyes should include treatments for mild and moderate dry eyes and additional therapy may include systemic anti-inflammatory agents, cholinergic, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and correction of any eyelid abnormalities.

Clinical Practice guidelines for treatment of conjunctivitis from the American Optometric Association (AOA) recommend the use of topical cyclosporine as an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Additionally, these guidelines state topical cyclosporine may be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy.

**RECOMMENDATION**

Cyclosporine ophthalmic emulsion is FDA approved to increase tear production in patients with keratoconjunctivitis sicca (KCS). Clinical trials are limited but demonstrate efficacy of cyclosporine ophthalmic emulsion. Clinical guidelines from the AAO recommend step therapy for the treatment of dry eye syndrome. The AAO recommends cyclosporine ophthalmic emulsion be used for moderate and severe dry eye syndrome after identified therapies for mild dry eye syndrome (e.g., artificial tears, compresses, etc.) have been utilized. The AOA clinical guidelines for treatment of conjunctivitis also recommend use of cyclosporine ophthalmic emulsion as alternative treatment to topical corticosteroids for severe atopic keratoconjunctivitis and for patients with vernal keratoconjunctivitis who have failed conventional therapy. Since clinical guidelines do not recommend this class of agents as first line therapy, it is recommended this class be subject to clinical criteria to ensure appropriate use.

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**RE-REVIEW: OPHTHALMIC IMMUNOMODULATORS**

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Clinical Criteria for Restasis:
Restasis will be approved for:
- Treatment of moderate to severe keratoconjunctivitis sicca (KCS) in patients who have failed at least ONE of the following therapies:
  - Polyvinyl alcohol Artificial tears drops or ointments administered at least QID four times daily (i.e. Refresh® Tears)
  - Carboxymethylcellulose artificial tears or ointments (i.e. Celluvisc®) administered at least four times daily.
  - Hydroxypropyl cellulose insert (Lacrisert®)
  - Punctal plugs
- Treatment of dry eyes in recipients with Sjogren’s disease
- Recipients using the agent status post corneal transplant
- Treatment of severe atopic keratoconjunctivitis who have tried and failed at least TWO ophthalmic steroids or have contraindication or intolerance to ophthalmic steroids.

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RE-REVIEW: OPHTHALMIC STEROIDS

BACKGROUND
- Ocular inflammation is a manifestation of cellular and vascular response of the host tissue to injury and involves a complex cascade of events. The pharmacological management of ocular inflammation involves administration of anti-inflammatory medications. Ophthalmic steroids are one medication class that is available for control and treatment of ocular inflammation.
- There is no generally accepted explanation for the mechanism of action of ocular steroids; however, they are thought to exert their anti-inflammatory activity by inhibiting phospholipase A2 and subsequently inhibiting both cyclooxygenase and lipoxygenase pathways.
With the exception of difluprednate and rimexolone, all of the agents in this class are FDA-approved for the treatment of steroid-responsive inflammatory ocular conditions. Difluprednate is approved for the treatment of post-operative inflammation and pain following ocular surgery. Rimexolone is approved for the treatment of post-operative inflammation as well as the treatment of chronic anterior uveitis. For a complete listing of FDA approved indications, refer to table 2 in the Med Metrics complete therapeutic class review.

The most common adverse events associated with the ophthalmic steroids include visual impairment, secondary ocular infections and increased intraocular pressure (IOP). Loteprednol is commonly associated with burning & itching upon instillation, and light intolerance. Rimexolone is commonly associated with headache, ocular pain and discharge. Less common, but serious adverse events associated with all ophthalmic steroids include perforation of the scleral globe, glaucoma, optic nerve damage and the formation of cataracts.

- Ophthalmic steroids are contraindicated in acute, untreated eye infections, in most viral diseases of the cornea and conjunctiva and also in ocular mycobacterial infections and fungal disease of ocular structures. Ophthalmic prednisolone sodium phosphate is contraindicated after uncomplicated removal of a superficial corneal foreign body.
- Prolonged use of ophthalmic steroids may result in ocular hypertension and/or glaucoma. The ability of a specific ophthalmic steroid to induce elevation of IOP is based on several factors including dosage, anti-inflammatory potency, and duration of treatment. Ophthalmic steroids should be used in caution in patients with glaucoma and intraocular pressure should be monitored routinely with the use of ten or more days. Ocular hypertension is generally reversible 1—3 weeks after steroid discontinuation; however, persistent pressure elevation with glaucoma and vision loss has occurred.
- The use of topical steroids may delay healing and increase the incidence of bleb formation after cataract surgery. Ophthalmic steroids may also suppress the host response and increase the hazard of secondary ocular infections when used for extended periods of time.
- Because ophthalmic medications have minimal systemic absorption, studies have not been conducted to assess drug interactions with the ophthalmic steroids.

Clinical Trials

- Ophthalmic loteprednol etabonate 0.5% when compared to ophthalmic prednisolone acetate 1% in two prospective, randomized-controlled trials (N=245) in patients with acute anterior uveitis, was found to be less effective in resolution of anterior chamber cell by day 28 (P=0.015). In both trials, an increase in IOP >10 mmHg was observed more frequently in the ophthalmic prednisolone acetate 1% group than the ophthalmic loteprednol etabonate 0.5% group (P value not reported).
- In a multi-study analysis of patients and subjects enrolled in domestic, double-blind, manufacturer-sponsored studies, loteprednol etabonate ophthalmic suspension was less likely than prednisolone acetate to cause clinically significant (10 mmHg or greater) increases in intraocular pressure (IOP) when used long-term. Among 2210 subjects and patients, 1648 received either loteprednol etabonate 0.2% or 0.5% (n=901), prednisolone acetate 1% (n=164), or placebo vehicle (n=583) for 28 days or longer. Known corticosteroid responders were excluded from all studies. The incidence of significantly increased IOP was 1.7% in the loteprednol group, 6.7% in the prednisolone group, and 0.5% in the placebo group. After excluding contact-lens wearers, the incidences were 0.6% in the loteprednol group, 6.7% in the prednisolone group, and 1% in the placebo group.
The safety and efficacy of ophthalmic rimexolone 1% was compared with ophthalmic prednisolone acetate 1% in patients with acute or chronic uveitis or recurrent iridocyclitis in three randomized-controlled trials. There were no significant differences in anterior chamber cell and flare scores between the two treatment groups and overall clinical efficacy was similar at the end of treatment (four weeks). More patients in the ophthalmic prednisolone acetate 1% group had an increase in IOP ≥10 mmHg compared to the patients in ophthalmic rimexolone 1% group (P value not reported). However, a study by Biswas et al (N=78) did not show any difference in the rise of IOP between the two topical steroids.

Ocular hypertensive and anti-inflammatory response of ophthalmic rimexolone 1% was compared to ophthalmic fluorometholone 0.1% in a randomized-controlled trial (N=54) in children four to eight years of age who underwent bilateral strabismus surgery. Net change in IOP was greater with ophthalmic rimexolone 1% compared to ophthalmic fluorometholone 0.1% (P<0.001).

Eighteen eyes in the ophthalmic rimexolone 1% group compared to fifteen eyes in the ophthalmic fluorometholone 0.1% group had an IOP >21 mmHg (P=0.53). There was a greater improvement in conjunctival inflammation on days 13 and 20 in the ophthalmic rimexolone 1% group compared to the ophthalmic fluorometholone 0.1% group (P=0.03).

Ophthalmic steroids have been utilized as first-line therapy in clinical practice since the 1950s for the treatment of ophthalmic inflammatory conditions. They are used in managing postoperative inflammation following various ocular surgeries, anterior uveitis, ocular allergies, external eye inflammatory diseases associated with some infections, corneal injury from chemical, radiation or thermal burns and penetration of foreign bodies. Although consensus guidelines do not recommend one particular ophthalmic steroid over another in the treatment of most ocular conditions, the American Optometric Association does recommend the use of ophthalmic prednisolone acetate 1% to control inflammation associated with anterior uveitis.

**RECOMMENDATION**

The ophthalmic steroids are FDA-approved for the treatment of steroid-responsive inflammatory ocular conditions, with the exception of difluprednate and rimexolone. Difluprednate is approved for the treatment of post-operative inflammation and pain following ocular surgery. Rimexolone is approved for the treatment of post-operative inflammation as well as the treatment of chronic anterior uveitis. Prolonged use of ophthalmic steroids may result in ocular hypertension and/or glaucoma. Results from clinical trials demonstrate that loteprednol is less likely than prednisolone acetate to cause clinically significant increases in intraocular pressure when used long-term. Currently available clinical guidelines do not recommend one particular ophthalmic steroid over another in the treatment of most ocular conditions; however, the American Optometric Association does recommend the use of ophthalmic prednisolone acetate 1% to control inflammation associated with anterior uveitis. Therefore, it is recommended that at least three ophthalmic steroids should be available for use, one of which should be prednisolone acetate. Additionally, due to the decreased relative risk of elevated intraocular pressure, loteprednol should be available for patients where a potential increase in intraocular pressure would place the patient at risk.

**COMMITTEE VOTE:**

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RE-REVIEW: OPHTHALMIC STEROIDS

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Clinical Criteria for Alrex®, Lotemax® & Vexol®

Alrex, Lotemaz or Vexol will be approved for recipients who meet ONE of the following criteria:

- Contraindication to any TWO of the preferred ophthalmic steroids, OR
- Concern that a potential increase in intraocular pressure (IOP) with preferred ophthalmic steroids would place patient at risk (i.e., glaucoma, pre-/post-cataract surgery, etc.)

SXC recommends removing the above clinical criteria.

COMMITTEE VOTE:

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References

RE-REVIEW: OPHTHALMIC ANTIVIRALS

BACKGROUND

- Keratitis, or corneal infection and inflammation, caused by herpes simplex virus (HSV) is a common and major cause of blindness. The HSV types associated with keratitis are HSV-1 and -2. The HSV-1 subtype is responsible for the majority of ocular lesions. There are four types of HSV keratitis and include infectious epithelial keratitis, stromal keratitis, endothelitis and neurotrophic keratopathy. Ocular herpes simplex virus (HSV) infections are characterized by a primary outbreak and subsequent recurrences. After the primary infection, HSV becomes latent in the trigeminal ganglion or the cornea and conditions such as stress, ultraviolet radiation, hormonal changes and use of topical ophthalmic medications can reactivate the virus. Lesions are common in immunosuppressed patients such as those with a recent organ transplant or with human immunodeficiency virus. Ophthalmic antiviral agents are one treatment option for ocular HSV; currently available agents include trifluridine and ophthalmic ganciclovir.

- Ophthalmic ganciclovir works as an antiviral agent by competitively inhibiting viral DNA polymerases and by incorporation into viral DNA resulting in chain termination.

- Trifluridine is incorporated in place of thymidine into viral DNA, resulting in faulty DNA and the inability to reproduce or to infect or destroy tissue.

- Ophthalmic ganciclovir is FDA approved for the treatment of acute herpetic keratitis (approved for patients 2 years and older).

- Trifluridine is FDA approved for primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV-1 and -2 (approved for patients 6 years and older).

- The most common adverse reactions seen with ophthalmic ganciclovir include blurred vision, conjunctival hyperemia, eye irritation, and punctuate keratitis. The most common adverse reactions seen with trifluridine include burning and stinging upon instillation, palpebral edema, and hyperemia.
  - Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ophthalmic ganciclovir.
  - Administration of ophthalmic trifluridine may cause mild local irritation of the conjunctiva and cornea when instilled, but these effects are usually transient.
  - There are no significant drug-drug interactions identified with the ophthalmic antivirals.

- Currently there are no head-to-head clinical trials of ophthalmic ganciclovir and ophthalmic trifluridine. As the older agent in the class, ophthalmic trifluridine has established safety and efficacy in the treatment of keratitis. When compared to acyclovir, which is not available as an ophthalmic dosage form, no significant difference between the two treatments in cure rates was found (90% vs 75%; $P$ value not reported). Additionally, both treatments were well tolerated. Ophthalmic ganciclovir has also demonstrated safety and efficacy in the treatment of keratitis, and when compared to acyclovir, no significant differences in healing rates were observed; however, treatment with ophthalmic ganciclovir did appear to be better tolerated.

- In addition, a Cochrane review (N=5,363) found that the use of ophthalmic vidarabine (discontinued), ophthalmic trifluridine, ophthalmic ganciclovir, or acyclovir resulted in improvement in most patients with keratitis within one week of treatment, with no treatment being significantly better than another.

- Ocular HSV infections are commonly treated with ophthalmic antiviral agents, mydriatics and oral acyclovir. The current clinical guidelines from the American Academy of Ophthalmology for the treatment of HSV conjunctivitis state that ophthalmic trifluridine and oral acyclovir are potential treatment options. It should be noted ophthalmic ganciclovir was FDA approved after these guidelines were published; therefore, it is not specifically addressed.
RECOMMENDATION
Keratitis, or corneal infection and inflammation, caused by herpes simplex virus (HSV) is a common and major cause of blindness. Ophthalmic antiviral agents are one treatment option for ocular HSV; currently available agents include trifluridine and ophthalmic ganciclovir. Currently there are no head-to-head clinical trials of ophthalmic ganciclovir and ophthalmic trifluridine. However, both agents have established safety and efficacy in the treatment of keratitis. The current clinical guidelines from the American Academy of Ophthalmology for the treatment of HSV conjunctivitis state that ophthalmic trifluridine and oral acyclovir are potential treatment options, the guidelines do not give preference to one agent over another. It should be noted ophthalmic ganciclovir was FDA approved after these guidelines were published. Therefore it is recommended that at least one ophthalmic antiviral agent be available for use.

COMMITTEE VOTE:

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References
BACKGROUND

- Blepharitis, conjunctivitis, and keratitis are common ophthalmic conditions characterized by inflammation, irritation and redness of the eye, eyelids and surrounding orbital areas. The ophthalmic conditions can be caused by various bacterial and viral organisms as well as fungal organisms. Ophthalmic antifungals are utilized when indicated by susceptible organisms. Currently the only available ophthalmic antifungal agent is natamycin.
- Natamycin exerts its antifungal effects by binding to sterols in the fungal cell membrane to produce a change in membrane permeability that allows loss of essential cellular constituents.
- Natamycin is indicated for the treatment of fungal blepharitis, conjunctivitis and keratitis caused by susceptible organisms including Fusarium solani keratitis.
- The most common adverse effects seen with natamycin eye irritation and hyperemia.
  - Failure of improvement of keratitis after 7 days should be re-evaluated for susceptibility to natamycin.
  - No drug interactions have been documented with ophthalmic natamycin.
- Ophthalmic natamycin has been compared to other topical antifungal agents; including econazole, itraconazole and voriconazole. It should be noted that econazole, itraconazole and voriconazole are not available in ophthalmic dosage forms. Results from these trials demonstrate no statistically significant differences between the agents in ulcer healing rates, clinical success, improvements in best spectacle-corrected visual acuity and scar size. Overall, treatment with ophthalmic natamycin was well tolerated.
- Ophthalmic natamycin is an established treatment option; however, the use of this agent is not specifically addressed within the clinical guidelines as the majority of the guidelines focus on the treatment of bacterial ocular infections.

RECOMMENDATION

Ophthalmic natamycin is approved for the treatment of fungal blepharitis, conjunctivitis and keratitis caused by susceptible organisms including Fusarium solani keratitis. In clinical trials, this agent is an established treatment option and has demonstrated similar safety and efficacy compared to other topical antifungal agents; however none of the agents compared to natamycin are available in an ophthalmic dosage form. None of the clinical guidelines regarding the ocular conditions for which ophthalmic natamycin is approved specifically address its role in treatment; however, when the infection is known to be caused by a susceptible organism, ophthalmic natamycin is appropriate. It is recommended that natamycin be available for use in ocular fungal infections.

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References

BACKGROUND

- Hypertension is a major national and international health concern. It is estimated that the prevalence of hypertension is one billion individuals worldwide. Although awareness, treatment and control of blood pressure are rising, high blood pressure remains a significant health problem. The Calcium Channel Blocker/Angiotensin II Receptor Blocker class contains combination products of amlodipine plus an angiotensin II receptor blocker (ARB) - olmesartan, telmisartan or valsartan - with or without the thiazide diuretic HCTZ.

- Amlodipine is a dihydropyridine calcium channel blocker and is a potent vasodilator due to its selectivity for vascular smooth muscle. The ARBs interfere with the renin-angiotensin-aldosterone system, which plays an influential role in blood pressure control. The binding of angiotensin II to its receptors results in vasoconstriction, as well aldosterone secretion. When these agents block the binding of angiotensin II, the resultant vasoconstriction and aldosterone release does not occur, therefore reducing blood pressure. Thiazide diuretics, including HCTZ, inhibit sodium reabsorption, causing increased excretion of sodium, water and potassium, resulting in lower blood pressure.

- The combination of amlodipine with either olmesartan, telmisartan or valsartan is FDA-approved for the treatment of hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals. The combination of amlodipine and HCTZ with either valsartan or olmesartan is FDA approved for the treatment of hypertension; however, neither combination is indicated for initial therapy.

- Adverse reactions most commonly associated with the ARB-CCB combos include edema, dizziness, headache and fatigue.
  - All ARB-CCB combination products carry a Black Box Warning against use during pregnancy due to the risk of injury and possible death to the developing fetus.
  - Hyperkalemia may develop while taking ARBs, particularly in patients with advanced renal impairment; heart failure; on renal replacement therapy or who are receiving potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels.
  - Use of calcium channel blockers in patients with heart failure should be done with caution.
  - Amlodipine/olmesartan carries a warning about vasodilation, especially if used in conjunction with a peripheral vasodilator. Additionally, decreases in hemoglobin and hematocrit may occur in patients treated with amlodipine/olmesartan.
  - Drug-drug interactions with the combination products are identical to the drug interactions with the individual components of the products.

- There are numerous clinical trials comparing combination therapy to monotherapy for the treatment of hypertension. In general, the trials demonstrated that combination therapy, administered either concomitantly or as a fixed dose combination is more effective than monotherapy. Currently no head-to-head clinical trials exist and no data is available to definitively demonstrate that one calcium channel blocker/ARB combination products is clinically superior to another or their individual components administered separately.
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure (JNC VII) recommends initial therapy using a thiazide-type diuretic for patients with uncomplicated hypertension. However, most patients will need at least two agents to control their blood pressure and the JNC VII recommends initial treatment with a combination of agents from different classes when blood pressure is greater than 20 mm Hg systolic or 10 mm Hg diastolic above goal. The use of combination drug regimens allows for lower doses of the individual agents which can reduce the potential for side effects. The JNC VII recommends specific agents based upon compelling indications and/or patient characteristics. ARBs are recommended as an alternative to ACE inhibitors in patients with the following compelling indications: heart failure, diabetes and chronic kidney disease.

RECOMMENDATION

The Calcium Channel Blocker/Angiotensin II Receptor Blocker class contains combination products of amlodipine plus an angiotensin II receptor blocker (ARB) with or without the thiazide diuretic HCTZ. All of the agents in this class are FDA-approved for the treatment of hypertension; though the combination products containing HCTZ are not indicated as initial therapy. Results from clinical trials demonstrate that combination therapy for the treatment of hypertension is more effective than monotherapy. Currently no head-to-head clinical trials exist and no data is available to definitively demonstrate that one calcium channel blocker/ARB combination product is clinically superior to another or their individual components administered separately. JNC VII recommends initial treatment with a combination of agents from different classes when blood pressure is greater than 20 mm Hg systolic or 10 mm Hg diastolic above goal. Additionally, JNC VII recommends ARBs in patients with heart failure, diabetes and chronic kidney disease. It is recommended that the ARB-CCB combination products should be subject to clinical criteria to ensure appropriate patient selection.

COMMITTEE VOTE:

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NEW: ARB-CCB COMBOS

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<td>Exforge® CC,QL (amlodipine/valsartan)</td>
<td>Azor® CC,QL (amlodipine/olmesartan)</td>
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<tr>
<td>Exforge HCT® CC,QL (amlodipine/valsartan/HCTZ)</td>
<td>Tribenzor® CC,QL (amlodipine/olmesartan/HCTZ)</td>
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<tr>
<td>Twynsta® CC,QL (amlodipine/telmisartan)</td>
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Clinical Criteria for Exforge® & Exforge HCT®

Will be approved for patients requiring combination therapy with an ARB and a calcium channel blocker who meet one of the following criteria:

- Diagnosis of hypertension, diabetic nephropathy, heart failure, left ventricular hypertrophy, chronic hyperkalemia, or renal insufficiency, OR
- Diagnosis of hypertension with a history of ACEI-induced angioedema, hypersensitivity to an ACEI, or inability to tolerate ACEI due to cough

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
Clinical Criteria for non-preferred ARB-CCB COMBOS

Will be approved for patients requiring combination therapy with an ARB and a calcium channel blocker who meet one of the following criteria:

- Diagnosis of hypertension, diabetic nephropathy, heart failure, left ventricular hypertrophy, chronic hyperkalemia, or renal insufficiency, AND are unable to take the products individually
- Diagnosis of hypertension with a history of ACEI-induced angioedema, hypersensitivity to an ACEI, or inability to tolerate ACEI due to cough, AND are unable to take products individually

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Quantity Limits

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<td>All other strengths: 1/day</td>
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COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References


RE-REVIEW: HEMOSTATIC AGENTS

BACKGROUND

- There are two agents in the therapeutic class review called “Hemostatic Agents”: aminocaproic acid and tranexamic acid. Both products are available in oral and injectable formulations; however, this review will focus on the use of the oral hemostatic agents.
- Aminocaproic acid and tranexamic acid are synthetic lysine analogs that act primarily by occupying the lysine binding sites on plasminogen, which inhibits the conversion of plasminogen to plasmin, and therefore fibrinolysis.
- Aminocaproic acid is FDA-approved for the treatment of acute bleeding syndromes to enhance hemostasis when fibrinolysis contributes to bleeding. Tranexamic acid tablets are FDA-approved for the treatment of cyclic heavy menstrual bleeding.
Oral aminocaproic acid and tranexamic acid are generally well tolerated. Diarrhea, dizziness, headache, and nausea are the most frequently reported adverse effects with aminocaproic acid. Abdominal pain, back pain, headache, and nasal and sinus symptoms are the most frequently reported adverse effects with tranexamic acid.

- Both agents have the potential to cause thromboembolic events. Aminocaproic acid is contraindicated when there is evidence of an active intravascular clotting process and in the presence of disseminated intravascular coagulation (DIC) without concomitant heparin. Tranexamic acid should not be prescribed to women who are known to have the following conditions: active thromboembolic disease, a history of thrombosis or thromboembolism, or an intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy).
- Aminocaproic acid should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risks of intrarenal obstruction secondary to glomerular capillary thrombosis or clots in the renal pelvis and ureters.
- Rare reports of skeletal muscle weakness with necrosis of muscle fibers with prolonged administration of aminocaproic acid. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure.
- Reports have appeared in the literature of an increased incidence of neurological deficits such as hydrocephalus, cerebral ischemia, or cerebral vasospasm associated with the use of antifibrinolytic agents in the treatment of subarachnoid hemorrhage. Cerebral edema and cerebral infarction may be caused by use of tranexamic acid in women with subarachnoid hemorrhage.
- Concomitant use of the hemostatic agents with estrogens or oral contraceptives may produce an increase in clotting factors leading to a hypercoagulable state.

Clinical trials
- Despite the fact that aminocaproic acid has been used to control various bleeding disorders over the past 30 years, there is limited published data evaluating the efficacy and safety of oral aminocaproic acid for its approved indications. Limited clinical studies and case reports have reported successes with the use of oral aminocaproic acid in patients with amegakaryocytic thrombocytopenia, hyperfibrinolysis and cirrhosis, hematuria, and menorrhagia.
- Tranexamic acid tablets were FDA-approved for the treatment of cyclic heavy menstrual bleeding based on efficacy and safety demonstrated in two randomized, placebo-controlled, double-blinded studies. Tranexamic acid (N=481), administered at a dose of 3,900 mg per day for up to 5 days during each menstrual cycle, significantly reduced menstrual blood loss as well as limitations on social, leisure, and physical activities compared to placebo.
- A meta-analysis of four clinical trials (N=193) reported that tranexamic acid (4,000 mg per day during the first 5 days of the menstrual cycle) produced a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo, flurbiprofen, mefenamic acid, and oral luteal phase progesterogens. Tranexamic acid was not associated with significantly more side effects than placebo or the other medical therapies; however, no trial measured thromboembolic events as an outcome.
- In a small trial comparing three different medical treatments for women with idiopathic menorrhagia, levonorgestrel-releasing intrauterine device was the most effective for reducing blood loss with reductions of 82% to 96% over 3 to 12 months compared to 44% for tranexamic acid and 21% for flurbiprofen.
Current guidelines from the American Academy of Family Physicians state the levonorgestrel-releasing intrauterine device (IUD) is an effective long-term option for the treatment of menorrhagia and that this option is more effective that continuous oral progestin therapy but less effective than endometrial ablation. Tranexamic acid tablets were not FDA-approved at the time of publication of this guideline; however, tranexamic acid has been used in other countries since 1966 for the treatment of menorrhagia. The National Collaborating Centre for Women’s and Children’s Health recommends treatment for heavy menstrual bleeding should be considered in the following order:
1) Levonorgestrel-releasing intrauterine system  
2) Tranexamic acid or nonsteroidal anti-inflammatory drugs (NSAIDs) or combination oral contraceptives  
3) norethindrone daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens. If hormonal therapy is not acceptable, tranexamic acid and NSAIDs are considered first-line treatment options.

Though not FDA-approved for use in patients with hemophilia, current guidelines from the World Federation of Hemophilia recommend the use of hemostatic agents for the treatment of GI bleeding and oral hemorrhage in specified patients with hemophilia. These products are also recommended as adjunctive therapy for mucosal bleeds and to decrease the use of coagulation products in dental extractions. This guideline does not differentiate between the available agents in this class.

**RECOMMENDATION**
The currently available oral hemostatic agents are aminocaproic acid and tranexamic acid. Aminocaproic acid is FDA-approved for the treatment of acute bleeding syndromes to enhance hemostasis when fibrinolysis contributes to bleeding and limited clinical studies and case reports have reported successes with its use. Tranexamic acid tablets are FDA-approved for the treatment of cyclic heavy menstrual bleeding. Clinical studies have reported that tranexamic acid was more effective than nonsteroidal anti-inflammatory drugs and luteal phase progestins in reducing heavy menstrual bleeding, but less effective than the levonorgestrel intrauterine device. The levonorgestrel intrauterine device is recommended by the National Collaborating Centre for Women’s and Children’s Health as first-line treatment for heavy menstrual bleeding if hormonal treatment is acceptable. Tranexamic acid, NSAIDs or combination oral contraceptives are recommended as second-line therapy. If hormonal therapy is not acceptable, tranexamic acid or NSAIDs are recommended. Due to its use in treating acute bleeding syndromes, it is recommended that aminocaproic acid should be available for use. Additionally, due to its use as second-line therapy for the treatment of heavy menstrual bleeding, it is recommended tranexamic acid tablets should be subject to clinical criteria.

**COMMITTEE VOTE:**

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<th>RE-REVIEW: HEMOSTATIC AGENTS</th>
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<tr>
<td>aminocaproic acid (compares to Amicar®)</td>
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<tr>
<td>Lysteda®</td>
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<tr>
<td><strong>Clinical Criteria for Lysteda®</strong></td>
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<tr>
<td>For the treatment of menorrhagia, approval of Lysteda requires patient must have tried and failed or have contraindication or intolerance to ALL of the following:</td>
</tr>
<tr>
<td>o Levonorgestrel-releasing IUD</td>
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<td>o At least two other forms of hormone therapy (oral, vaginal, topical or injectable estrogen and/or progesterone)</td>
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<td>o NSAIDs</td>
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<td>All other diagnoses require trial and failure, intolerance or contraindication to aminocaproic acid.</td>
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### Quantity Limits

| Lysteda<sup>®</sup> QC | 30 tabs/28 days |

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### References

RE-REVIEW: ANTI-EMETICS: ANTICHOLINERGICS

BACKGROUND

- The pathophysiology of nausea and vomiting is complex and involves multiple neurotransmitters and organ systems which are all coordinated by the central nervous system. Dopamine, serotonin, histamine and substance P are the neurotransmitters believed to play the largest role. Nausea and vomiting, due to central or vestibular disorders, respond well to anticholinergic agents and histamine-1 receptor antagonists. This class review encompasses meclizine, prochlorperazine, promethazine, scopolamine and trimethobenzamide and will focus primarily on their use as anti-emetics.
- All of the agents in this class possess anti-emetic properties and share a similar mechanism of action in that all act centrally affecting the chemotrigger zone.
- Meclizine is FDA-approved for the treatment of motion sickness-related nausea and vomiting and peripheral vertigo. Prochlorperazine is classified as a piperazine phenothiazine antipsychotic and is FDA-approved for the treatment of schizophrenia and generalized anxiety, in addition to the treatment of nausea and vomiting. Promethazine has multiple FDA-approved indications ranging from allergic conditions to sedation to nausea and vomiting. (For a complete listing of promethazine’s indications see table 2 in the Med Metrics class review) Scopolamine is approved for the prevention and treatment of motion-sickness related nausea and vomiting. Additionally, transdermal scopolamine is FDA-approved for the management of postoperative nausea and vomiting.
- Adverse events reported with most of the agents in this class include blurred vision, changes in blood pressure, confusion, dizziness, drowsiness, dry mouth and extrapyramidal symptoms. Adverse events associated with phenothiazines, which could potentially occur with prochlorperazine, include increases in serum prolactin levels, resulting in galactorrhea; pituitary tumors; urinary discoloration; urinary incontinence and weight gain.
  - Promethazine is contraindicated in patients less than two years of age and carries a Black Box Warning regarding such use due to the potential for fatal respiratory depression in this patient population.
  - Prochlorperazine is contraindicated in patients in combination with large amounts of CNS depressants, in pediatric surgery patients and in patients less than two years of age or weight less than 20 pounds. Prochlorperazine and promethazine are contraindicated in patients in a comatose state. Scopolamine is contraindicated in patients with angle-closure glaucoma. Oral scopolamine is contraindicated in patients with impaired renal or hepatic function, prostatic hypertrophy and pyloric obstruction.
  - Due to their anticholinergic properties meclizine, prochlorperazine, promethazine and scopolamine should be used with caution in patients with chronic bronchitis, concomitant asthma, emphysema, glaucoma, prostatic hypertrophy or any condition that may be exacerbated by anticholinergic activity. Prochlorperazine carries a precaution about its risk of α-adrenergic blockade, elevated prolactin levels, extrapyramidal symptoms, tardive dyskinesia and the risk of producing a false-positive phenylkeouria test. Promethazine carries a precaution about the risk of bone marrow depression, central nervous system depression, decreased seizure threshold, neuroleptic malignant syndrome and respiratory depression. Precaution should be taken if trimethobenzamide is administered to children for the treatment of vomiting, due to risk of extrapyramidal symptoms and potentially hepatotoxic effects if the patient concomitantly has Reye’s syndrome.
  - The anti-emetic: anticholinergics should be used with caution in patients receiving concomitant therapy with anticholinergics because of additive effects. Additionally, due to the potential for additive sedative effects, their use with central nervous system depressants should be done with caution.
Clinical trials have demonstrated these agents to be useful and effective for the prevention of nausea and vomiting. However, head-to-head trial data between the agents in this class for the prevention and/or treatment of nausea and vomiting are lacking.

- In a crossover trial evaluating scopolamine transdermal patch, meclizine and placebo for the treatment of motion sickness, Dahle et al demonstrated that scopolamine transdermal patch was more effective than both placebo and meclizine.
- Similar results are reported in a meta analysis conducted by Spinks et al which demonstrated that scopolamine was more effective than meclizine and that the scopolamine transdermal patch specifically, was as effective as promethazine and dimenhydrinate.

In their medical position statement regarding nausea and vomiting, the AGA states that motion sickness and related disorders are treated primarily with histamine H₁ and cholinergic receptor antagonists (e.g., scopolamine). Since oral scopolamine has a short duration of action and a high incidence of side effects, oral therapy usually has been reserved for prophylactic treatment of patients exposed to short periods of intense motion or those who are highly susceptible to motion sickness. Antihistamines or other drugs have generally been preferred for the prevention of motion sickness in patients with prolonged exposure to mild to moderate motion. The transdermal delivery of scopolamine is highly effective for the prevention of motion sickness with a longer duration of action and fewer side effects than the oral formulation.

The American College of Obstetricians and Gynecologists considers antihistamines, benzamides (trimethobenzamide) and phenothiazines as safe and effective in treating nausea and vomiting associated with pregnancy.

Although there is limited data available, agents within this class have additional Food and Drug Administration approved indications outside their use as anti-emetic therapies. It should be noted that none of the associated clinical guidelines specifically address the role of any of these agents.

**RECOMMENDATION**
The anti-emetic anticholinergic agents are FDA-approved for the management of nausea and vomiting. Clinical trials have demonstrated these agents to be useful and effective for the prevention of nausea and vomiting. The American College of Obstetricians and Gynecologists considers antihistamines, benzamides and phenothiazines as safe and effective in treating nausea and vomiting associated with pregnancy. In their medical position statement regarding nausea and vomiting, the AGA states that motion sickness and related disorders are treated primarily with histamine H₁ and cholinergic receptor antagonists. Results from clinical trials verify that transdermal scopolamine is an effective treatment option for the prevention of motion sickness; however, due to the incidence of adverse events, antihistamines or other drugs have generally been preferred for the prevention of motion sickness. It is recommended at least two anti-emetic anticholinergic agents should be available for use. Additionally, transdermal scopolamine should be subject to clinical criteria to restrict its use to patients who are unable to take other short-acting agents.

**COMMITTEE VOTE:**
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- DISAPPROVED
- APPROVED with MODIFICATION
RE-REVIEW: ANTI-EMETICS: ANTICHOLINERGICS

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Clinical Criteria for Transderm-Scop®
Prior Authorization for Transderm-Scop® will be approved if recipient meets ANY of the following criteria:
- Trial and failure, or intolerance to, one of the following: meclizine, promethazine, dimenhydrinate, diphenhydramine, or metoclopramide
- Unable to take oral medication
- Will be in an area/situation for an extended period of time where taking short acting agents would not be feasible

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

Quantity Limits
Transderm-Scop® 4 patches per 30 days

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Tigan®/trimethobenzamide
Prior authorization not required for recipients ≤ 2 years of age. Drug not covered in patients > 2 years old.

SXC recommends removal of the above clinical criteria.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

References
NEW: SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATOR

BACKGROUND

- Multiple sclerosis (MS) is a neurological condition involving episodes of inflammation within the brain and spinal cord, resulting in scarring and removal of the insulating myelin sheath covering the nerves. Areas of scar tissue form along nerve fibers, slowing or blocking the transmission of signals to and from the brain and spinal cord.
- Fingolimod acts as a functional antagonist at the sphingosine 1-phosphate receptor, resulting in reduced lymphocyte migration. The antagonism produced by fingolimod reduces the infiltration of auto-aggressive lymphocytes from the lymph nodes into the central nervous system. In addition, fingolimod may also act at the same receptor to promote neuroprotective and reparative processes within the central nervous system.
- Fingolimod is FDA approved for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
- The most common adverse effects seen with fingolimod are diarrhea, increased liver enzymes, backaches, headaches, cough, and influenza like symptoms. More severe adverse effects include atrioventricular block, bradycardia, retinal edema, and lymphocytopenia.
  - A decrease in heart rate after initiation of fingolimod has been reported. With continued dosing, the heart rate returns to baseline within one month of chronic treatment. Treatment initiation with fingolimod has also resulted in transient atrioventricular conduction delays which resolved within the first 24 hours of treatment in clinical trials.
  - Ophthalmologic evaluations should be performed at baseline and three to four months after treatment is started to evaluate the presence and severity of macular edema, patients with existing uveitis and diabetes should use caution due to disease states causing baseline increase in risk of macular edema.
  - Fingolimod causes a dose-dependent reduction in peripheral lymphocyte count to 20 to 30% of baseline values; treatment may increase the risk of infections.
  - Women of childbearing potential should use effective contraception to avoid pregnancy during and for two months after stopping treatment with fingolimod.
  - Concomitant use of fingolimod and Class IA or III antiarrhythmics may result in serious heart rhythm disturbances and an increased risk of developing bradycardia or heart block.
- The two pivotal clinical trials demonstrating the safety and efficacy of fingolimod include a placebo- and an active-controlled trial with interferon β.
  - Compared to placebo, annualized relapse rates with fingolimod were significantly less, with a relative reduction of 54 to 60% (P<0.001). In contrast with previous trials, results from this trial demonstrated that treatment with fingolimod reduced the risk of disability progression, and Expanded Disasability Status scores remained stable or improved slightly in fingolimod-treated patients while worsening with placebo (P<0.02). All MRI outcomes compared to placebo demonstrated consistent benefits of fingolimod treatment.
  - In the active-controlled trial comparing treatment with fingolimod to interferon β, annualized relapse rates were significantly lower with fingolimod (0.16 to 0.20 vs 0.33; P<0.0001). In this trial, progression of disability was infrequent in all the treatment groups, with no significant differences between treatment groups in the time to the progression of disability or in the proportion of patients with confirmed progression.
General approaches to treatment of MS include the management of symptoms, the management of emotional and social consequences of relapses and disability, the treatment of acute episodes with corticosteroids and treatment with disease modifying agents. Specifically, disease modifying agents aim to reduce the frequency and/or severity of relapses and/or to slow disease progression. Currently available clinical guidelines from NICE and the MS Society recommend interferon β or glatiramer as disease modifying therapies. Due to its recent FDA approval, the role of fingolimod in the treatment of MS is not addressed within current clinical guidelines.

**RECOMMENDATION**

Fingolimod is the first FDA approved sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. In clinical trials, fingolimod significantly reduced relapse rates in patients with relapsing-remitting MS compared to both placebo and interferon β; however no significant difference was detected in the time to progression of disability or in the proportion of patents with confirmed progression. A Risk Evaluation and Mitigation Strategy is in place to inform patients and health care providers about the serious risks associated with this agent, including bradyarrhythmias and atrioventricular block, infections, macular edema, respiratory effects, hepatic effects and fetal risk. Current clinical guidelines recommend initiation of treatment with an interferon B or glatiramer as soon as possible following a definite diagnosis of MS with active, relapsing disease. As it is a recently FDA approved agent, the role of fingolimod in the treatment of MS is not addressed within current clinical guidelines. Due to the limited clinical experience and head-to-head data with established therapies, as well as its specific FDA approved indication and significant adverse event profile, it is recommended that fingolimod be subject to clinical criteria.

**COMMITTEE VOTE:**

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**Clinical Criteria for Gilenya®:**

Gilenya will be approved for recipients with a diagnosis of relapsing, remitting Multiple Sclerosis (RRMS) who meet the following criteria:
- Trial and failure of interferon β or glatiramer
- Contraindication, drug-drug interaction, or intolerance to BOTH interferon β or glatiramer

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

**Quantity Limits:**

Gilenya® 1 per day

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
References

BACKGROUND

- Potassium has many physiologic functions within cells, including protein and glycogen synthesis and cellular metabolism and growth. It is also a determinant of the electrical action potential across the cell membrane. A serum potassium concentration outside the normal range is associated with significant consequences on neuromuscular activity, in particular cardiac conduction. Other clinical manifestations include severe muscle weakness or rhabdomyolysis, cardiac arrhythmias, electrocardiograph abnormalities, renal abnormalities and glucose intolerance. Hypokalemia (serum potassium concentration <3.5 mEq/L) is one of the most common electrolyte abnormalities seen in clinical practice. The severity of the clinical manifestations associated with hypokalemia tends to be proportionate to the degree and duration of the reduction in serum potassium. Most common causes of hypokalemia include decreased dietary intake of potassium; increased translocation of potassium into cells or, most often, increased losses of potassium in the urine (diuretic therapy), gastrointestinal tract (vomiting or diarrhea) or sweat.

- The goals of hypokalemia management are to prevent the development of and treat serious life-threatening complications by normalizing the serum potassium concentration and preventing overcorrection and to identify and correct the underlying cause of hypokalemia. The general approach to the treatment of hypokalemia depends on the degree and rapidity in which the condition developed and the presence of symptoms. Potassium supplementation should be initiated in patients with a serum potassium concentration between 3.0 and 3.5 mEq/L with underlying cardiac conditions, as these patients are at a higher risk for cardiac arrhythmias. Patients with serum potassium concentration <3.0 mEq/L should be treated to achieve serum potassium values between 4.0 and 4.5 mEq/L. Oral administration of potassium supplementation is preferred; however, intravenous administration may be required in symptomatic patients.

- Potassium bicarbonate and potassium chloride are both used for prevention and treatment of hypokalemia.
  - Potassium chloride is primarily used in the treatment of hypokalemia because it is most effective in potassium depletion; this condition is associated with a loss of both potassium and chloride. Potassium chloride is available in generic capsules, tablets and liquid formulations as well as two slow-release oral tablets, a wax-matrix formulation and microencapsulated formulation. Slow release products are better tolerated than liquid formulations as patients often discontinue liquid due to unpleasant taste; however, there have been reports of intestinal and gastric ulceration and bleeding with the extended-release preparations. Therefore, extended-release potassium chloride preparations should be reserved for those patients who cannot tolerate, refuse, or patients in whom there is a problem of compliance with liquid or effervescent potassium preparations.
  - Potassium bicarbonate is preferred in the metabolic acidosis setting; it’s available in generic effervescent tablets.

- Potassium is actively transported into cells through a process facilitated by dextrose, insulin, and oxygen. Transport maintains a high potassium gradient across cell membranes, thus playing a vital role in conduction of nerve impulses in heart, brain, skeletal muscle; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion.

- Potassium chloride and potassium bicarbonate are FDA approved for the prevention and treatment of hypokalemia or digoxin toxicity associated with hypokalemia.

- The most common adverse reactions related to potassium supplements in patients with hypokalemia are rash, hyperkalemia, abdominal pain/discomfort, diarrhea, flatulence, GI bleeding, GI obstruction, GI perforation, nausea and vomiting.
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration can produce cardiac arrest. Solid oral dosage forms of potassium are contraindicated in patients whom there is a structural, pathological, and/or pharmacologic cause for delay or arrest in passage through the GI tract.

In patients with impaired mechanisms for excreting potassium, the administration of potassium supplements can produce hyperkalemia and cardiac arrest. The use of potassium supplements in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

Caution should be used in patients with acid/base alterations, cardiovascular disease, and disorders or conditions likely to contribute to altered serum potassium and hyperkalemia.

Potassium supplements concomitantly administered with eplerenone will increase potassium serum concentrations, which may increase the risk of hyperkalemia and associated serious arrhythmias. Potassium supplements may enhance hyperkalemic effects of potassium-sparing diuretics, ACE inhibitors, and Angiotensin II receptor blockers. Anticholinergics may increase risk for GI irritation with extended release oral dosage formulations of potassium salts.

Potassium supplementation is a well established treatment option for the management of hypokalemia; however, the clinical trial information demonstrating its safety and efficacy is limited. Wuermser and colleagues performed a double blind, randomized controlled trial comparing potassium magnesium citrate 3 tablets (42 mEq potassium, 21 mEq magnesium, 63 mEq citrate/day) twice daily plus HCTZ 50mg /day to potassium chloride 3 tables (42 mEq potassium/day) twice daily plus HCTZ. The study was conducted in 2 phases: Phase I HCTZ alone, Phase II HCTZ was provided with potassium supplements. Patients were instructed on a diet with a daily composition of approximately 45 to 55 mEq potassium, 160 to 200 mg (13.2 to 16.4 mEq) magnesium, 90 to 120 mEq sodium, 120 to 150 mEq chloride and 3 L fluids. Primary end points were blood and urinary parameters with secondary end point safety.

- The mean urinary pH did not change significantly on HCTZ alone. It increased significantly when potassium magnesium citrate was added to HCTZ by about 0.6 (P<0.001) however, there were no significant change in urinary pH with potassium chloride supplementation. Differences between the two groups were significant (P<0.0001).
- Urinary citrate decreased significantly in both groups during HCTZ alone however it increased with potassium magnesium but not with potassium chloride. Between groups differences during supplementation were significant (P=0.0004).
- Urinary magnesium increased significantly following supplementation with potassium magnesium citrate (P<0.01), but did not change significantly after potassium chloride supplementation. Differences between the two groups were significant (P=0.0007).
- Urinary potassium increased significantly following supplementation with potassium magnesium citrate (P<0.001) and potassium chloride (P<0.05).
- No significant difference in frequency and severity scores for any side effect was disclosed between HCTZ alone and the supplementation phase in either group. HCTZ alone, individual scores for muscle weakness, muscle cramping and dizziness increased significantly however muscle weakness and cramping decreased with potassium magnesium citrate from HCTZ alone (P=0.05) and muscle weakness and dizziness declined significantly following potassium chloride supplementation (P=0.05).
The National Council on Potassium in Clinical Practice: New Guidelines for Potassium Replacement in Clinical Practice recommend potassium supplements for individuals sensitive to sodium who are unable or unwilling to reduce salt intake and those who are subject to nausea, vomiting, diarrhea, bulimia or diuretic/laxative abuse. Potassium supplements are recommended in patients with drug related hypokalemia and routinely considered in patients with CHF, even if the initial potassium determination appears to be normal.

RECOMMENDATION
Although the clinical trial information demonstrating safety and efficacy of potassium supplementation is limited, it is a well established treatment for management of hypokalemia. According to the National Council on Potassium in Clinical Practice, potassium supplements are recommended for treatment and prevention of hypokalemia. Potassium chloride and potassium bicarbonate both are FDA approved for the prevention and treatment of hypokalemia or digoxin toxicity associated with hypokalemia. Potassium chloride is the most effective treatment for the common causes of potassium depletion and potassium bicarbonate is preferred when potassium depletion occurs in the setting of metabolic acidosis. Therefore, it is recommended that both potassium chloride and potassium bicarbonate should be available for use.

COMMITTEE VOTE:
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References
RE-REVIEW: POTASSIUM DEPLETERS

BACKGROUND

- Potassium is the primary intracellular cation found in the human body and has many physiologic functions within cells, including protein and glycogen synthesis and cellular metabolism and growth. Potassium plays a major role in muscle and nerve cell electrodynamics. A serum potassium concentration outside the normal range is associated with significant consequences on neuromuscular activity, specifically in cardiac conduction. Although hyperkalemia (serum potassium concentration >5.5 mEq/L) is not as common as hypokalemia (serum potassium concentration <3.5 mEq/L). Associated clinical manifestations of hyperkalemia include muscular weakness or flaccid paralysis, ileus and characteristic electrocardiograph (ECG) changes. The clinical manifestations associated with this disorder can cause significant consequences in patients and may require immediate treatment. In this review we will focus on the potassium depleter sodium polystyrene sulfonate, used for the treatment of hyperkalemia.

- Potassium enters the body via oral dietary intake or intravenous infusion and is stored in cells until excreted in the urine. There are four primary causes of hyperkalemia which include an increased dietary intake of potassium, decreased potassium excretion, renal tubular unresponsiveness to aldosterone and redistribution of potassium into the extracellular space. The kidneys typically eliminate 80% of the daily potassium intake. Therefore in the case of renal insufficiency (e.g., acute renal failure or chronic kidney disease) the kidney’s ability to excrete potassium is impaired. Clinical conditions (e.g. sickle cell anemia, systemic lupus) that cause tubular unresponsiveness to aldosterone and a decrease in urinary excretion of potassium ultimately result in hyperkalemia. The redistribution of potassium into the extracellular space could occur in conditions such as metabolic acidosis and diabetes mellitus or as a result of drugs such as beta blockers that could also cause transcellular potassium shifts in the body.

- Hyperkalemia management goals focus on counteracting the adverse cardiac effects, reversing current symptoms and returning serum concentration and total body stores of potassium to normal. Asymptomatic patients with mild (serum potassium concentration 5.5 to 6.0 mEq/L) hyperkalemia do not require specific therapy. Symptomatic patients with moderate (serum potassium concentration 6.1 to 6.9 mEq/L) to severe (serum potassium concentration >7.0 mEq/L) hyperkalemia, require immediate treatment. Initial treatment should focus on the antagonism of the cardiac membrane actions of hyperkalemia and once hemodynamically stable, the focus of treatment should shift to the reduction of extracellular and total body potassium concentrations.

- Sodium polystyrene sulfonate is FDA (Food and Drug Administration) approved for the treatment of hyperkalemia. Sodium polystyrene sulfonate is a cation-exchange resin that removes potassium by exchanging sodium ions for potassium ions as it passes through the intestines. Specifically, each gram of sodium polystyrene sulfonate exchanges 1 mEq of sodium for 1 mEq of potassium ions.


The most common adverse drug events include anorexia, nausea, vomiting, constipation, diarrhea, gastric irritation, hypocalcemia, hypokalemia and sodium retention. More serious gastrointestinal (GI) events include cases of colonic necrosis, bleeding and ischemic colitis or perforation. These severe cases of GI events reported were associated with the utilization of Kayexalate® and involved the concomitant use of sorbitol. As a result, the use of sorbitol along with sodium polystyrene sulfonate is not recommended.

- There are no black box warnings reported for this agent. However, sodium polystyrene sulfonate is an absolute contraindication in patients that have a GI obstruction or in patients that have hypokalemia.
- Patients receiving sodium polystyrene sulfonate should be monitored for all applicable electrolyte disturbances as sodium polystyrene sulfonate is not selective for potassium in its actions and small amounts of other cations, such as magnesium and calcium, may also be lost during treatment. Precautions should also be taken in patients who are unable to tolerate small increases in sodium loads (i.e., severe congestive heart failure, severe hypertension or marked edema) and compensatory restriction of sodium intake from other sources may be required.
- Concomitant use of sodium polystyrene sulfonate in renal impaired patients with aluminum, magnesium hydroxide, or calcium carbonate antacids may result in unanticipated metabolic alkalosis and a reduction of the resin's binding of potassium.

Sodium polystyrene sulfonate was approved by the FDA in 1958, prior to the date for which efficacy data for pharmaceutical products were required for approval and marketing; therefore, clinical trial data demonstrating the safety and efficacy of sodium polystyrene sulfonate in the treatment of hyperkalemia is very limited. Additionally, the safety and efficacy in pediatric patients has not been established. Nonetheless, in two studies conducted in 1961, the serum potassium levels fell by at least 0.4 mEq/L in the first 24 hours in 23 out of 30 patients and all seven patients who were treated with three daily doses of sodium polystyrene sulfonate in sorbitol had a gradual and steady decrease in serum potassium over five days.

There are no clear clinical guidelines for the treatment of hyperkalemia. The optimal therapy regimen for a given patient is primarily based on the quickness and degree of lowering that is necessary to reverse symptoms and return serum concentrations and total body stores of potassium to normal.

**RECOMMENDATION**
Potassium plays a major role in muscle and nerve cell electrodynamics. A serum potassium concentration outside the normal range is associated with significant consequences on neuromuscular activity, specifically in cardiac conduction. The goals of hyperkalemia management are to counteract adverse cardiac effects, reverse any symptoms that are present and return the serum concentration and total body stores of potassium to normal. Products containing the potassium depleter sodium polystyrene sulfonate are used for the treatment of hyperkalemia and works to reduce total body serum potassium concentrations. Therefore it is recommended that at least one sodium polystyrene sulfonate product be available for use.

**COMMITTEE VOTE:**
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### RE-REVIEW: POTASSIUM DEPLETERS

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BACKGROUND
- Wilson’s disease is an inherited, autosomal recessive disorder of copper metabolism. This disorder primarily involves impairment of biliary copper excretion which results in copper accumulation that will ultimately cause liver and brain toxicity. Wilson’s disease requires lifelong treatment. Treatment may be divided into two phases: initial (removal of accumulated copper) and maintenance (prevention of re-accumulation of copper). Wilson’s disease typically presents clinically within the second or third decades of life. Liver copper toxicity may present as hepatitis, chronic cirrhosis or liver failure. While brain copper toxicity presents as a movement disorder or psychiatric disturbances. This class review will focus primarily on zinc prescription products (i.e. zinc sulfate and zinc acetate). There are currently three Food and Drug Administration (FDA) approved medications to treat Wilson’s disease: Cuprimine® (D-penicillamine), Syprine® (trientine) and Galzin® (zinc acetate). Agents used primarily in the initial phase of Wilson’s disease include D-penicillamine and trientine, classified as chelating agents to assist with the renal excretion of copper.
- In addition to zinc acetate, zinc is also available orally as zinc sulfate. Both salt forms have a similar mechanism of action (MOA) and are considered effective in the treatment of Wilson’s disease. D-penicillamine and trientine are often preferred over zinc for treatment of copper accumulation, however, because complete copper blockade with zinc takes approximately 2 weeks to occur. Therefore, zinc is reserved primarily for maintenance therapy to prevent re-accumulation of copper. Zinc therapy may also be used in the acute phase in combination with D-penicillamine or trientine. Pregnant and pre-symptomatic patients may also be treated with zinc.
- Zinc blocks the absorption of copper via entering the intestinal cells and producing an endogenous chelator known as metallothionein. As the amount of metallothionein increases in the body it complexes with the copper entering the intestinal cells and prevents the reabsorption of copper into the bloodstream. Furthermore, as the intestinal cells die, they slough into the lumen of the bowel, removing the complexed copper with it in the stool.
- Galzin® (zinc acetate) is FDA approved for the maintenance treatment of Wilson’s disease for patients who have initially been treated with a chelating agent. The trace element, zinc sulfate has not been evaluated by the Food and Drug Administration; however it is well established that zinc sulfate and other available zinc salts are efficacious in the management of zinc deficiency.
Adverse events for zinc acetate include elevations in alkaline phosphatase, amylase and lipase. Gastric irritation is another common adverse event experienced by utilization of zinc acetate. Adverse events of zinc sulfate include dizziness, diarrhea, nausea, gastric ulcers, vomiting and restlessness. Additionally, deaths have been reported with the use of zinc sulfate following an overdosage and in a patient with advanced liver disease and hemolytic crisis where zinc sulfate was used as initial treatment.

- Zinc acetate is contraindicated in patients with known hypersensitivity to any of the components of the formulation. There are no reported contraindications for zinc sulfate in the clinical literature.
- No documented drug interactions associated with zinc acetate are reported in the clinical literature.
- Clinical trial information demonstrating zinc's safety and efficacy is limited. The majority of the trials are primarily reports rather than placebo controlled trials due to the nature of the disease and availability of effective treatments. Furthermore, most of the clinical trial experience regarding zinc in the treatment of Wilson's disease has focused on maintenance therapy following treatment with a chelator. Extensive clinical trial data also does not exist for zinc used as primary treatment, in patients who developed worsening neurologic symptoms with D-penicillamine (chelating agent), during pregnancy or in young children.
  - In a dose finding report of pediatric patients with Wilson's disease, zinc acetate 25 mg twice daily, 25 mg three times daily and 50 mg three times daily all met the efficacy objectives of copper control, zinc levels, neurologic improvement and maintenance of liver function. Results from this trial support the use of zinc acetate for the treatment of pediatric patients with Wilson's disease.
  - A second report from Brewer et al supports the evidence demonstrating that the use of zinc acetate during pregnancy is not harmful to the women or the fetus. In this small report (N=19), 26 pregnancies of women with Wilson's disease who were receiving zinc acetate were followed. Copper levels were well maintained throughout and in the evaluated pregnancies, liver function data and neurologic and/or speech scores demonstrated stability. In total, one major and one minor fetal abnormality was observed among the 26 pregnancies and the authors were aware of four miscarriages.
  - Additionally, in a report of 17 symptomatic patients, treatment with zinc Therapy (zinc acetate, sulfate) only demonstrated effectiveness for neurologic disease versus hepatic disease. Therefore exhibiting long-term zinc therapy is effective in managing the neurological symptoms of Wilson's disease.

Zinc sulfate, a well established trace element is used for the management of zinc deficiency. Zinc acetate, available only as a branded product Galzin®. Galzin® is Food and Drug Administration (FDA) approved for maintenance treatment of patients with Wilson’s disease who have been initially treated with a chelating agent. Although Galzin® (zinc acetate) was the first zinc salt formulation to receive FDA approval for the treatment of Wilson's disease, zinc therapy effectiveness in this disease state is well established. The abilities in which zinc sulfate and zinc acetate interfere with copper absorption to treat Wilson's disease are very similar. However, the tolerability between the agents differs. Specifically, zinc acetate has been associated with less gastrointestinal side effects versus zinc sulfate.
RECOMMENDATION

Wilson’s disease is a disorder characterized by impaired biliary copper excretion which ultimately results in copper accumulation within the body. Wilson’s disease is a lifelong medical condition with 2 phases of treatment: Initial therapy (removal of accumulated copper) and maintenance therapy (prevention of re-accumulation of copper). Medications used in the treatment of Wilson’s disease include chelating agents and zinc. Although Galzin® (zinc acetate) is the first zinc salt formulation to receive FDA approval for the treatment of Wilson’s disease, zinc therapy effectiveness in this disease state is well established. Zinc treats Wilson’s disease via the blockade of copper absorption. Complete copper blockade with zinc takes approximately 2 weeks to occur, and is therefore reserved for maintenance therapy to prevent re-accumulation of copper. Zinc may also be used in the acute phase of treatment in combination with chelating agents.

The American Association for the Study of Liver Disease: Diagnosis and Treatment of Wilson Disease: 2008 Update recommends a chelating agent or zinc be used for the treatment of pre-symptomatic patients or those on maintenance therapy. The mechanisms of action by which zinc sulfate and zinc acetate interfere with copper absorption to treat Wilson’s disease are very similar. In addition, the guidelines do not differentiate between the two agents; however, zinc acetate has been associated with less gastrointestinal side effects. Therefore it is recommended that at least one zinc agent be made available, with zinc acetate reserved for those patients experiencing GI intolerance to zinc sulfate.

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RE-REVIEW: ZINC SUPPLEMENTS

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Clinical Criteria for Galzin® (zinc acetate)

Will be approved for the following:
- a diagnosis of Wilson’s disease and an intolerance to zinc sulfate

COMMITTEE VOTE:

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References

RE-REVIEW: VITAMIN K

BACKGROUND

- Vitamin K is an essential dietary nutrient that regulates the synthesis of clotting factors and is found naturally in two forms: vitamin K₁ and K₂. Vitamin K₁ is also available in a synthetic form (phytonadione) which has the same activity as its naturally occurring counterpart. This review will focus on the oral vitamin K product available by prescription.
- Phytonadione possesses the same type and degree of activity as naturally-occurring vitamin K₁, which is necessary for the complete hepatic synthesis of the plasma coagulation factors II, VII, IX and X.
- Phytonadione is FDA-approved for anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives, hypoprothrombinemia secondary to antibacterial therapy, hypoprothrombinemia secondary to administration of salicylates, and hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas but only if bile salts are administered concurrently.
- Adverse drug events for orally administered phytonadione are not reported in the clinical literature.
  - An immediate coagulant effect should not be expected after administration of phytonadione, and the medication will not counteract the anticoagulant action of heparin. Dosages should be kept as low as possible, and INR should be checked regularly as clinical conditions indicate.
  - No significant drug interactions associated with oral phytonadione are reported in the clinical literature. Temporary resistance to prothrombin-depressing anticoagulants may result with phytonadione treatment, especially when larger doses of the medication are used.
- Clinical trial data demonstrating the safety and efficacy of vitamin K in correcting excessive coagulation in patients receiving warfarin is limited.
  - Results from a case series (N=81) of patients on warfarin presenting with an episode of excessive anticoagulation (international normalized ratio [INR] >5.0) demonstrated that withholding one or two doses of warfarin and administering 2.5 mg of vitamin K is an effective method for correcting excessive anticoagulation. The evaluated patients all had an INR <10.0 and had no serious bleeding episodes.
  - A placebo-controlled trial confirmed these results, as the addition of vitamin K 2.5 mg significantly reduced the time to achieve an INR of 4.0 by approximately one day compared to omitting warfarin therapy alone. The safety was comparable between treatment groups; there were no thromboembolic events or major bleeding complications in either group.
  - Another small placebo-controlled trial evaluated the administration of vitamin K to placebo in patients with a mechanical heart valve receiving warfarin therapy who presented with an INR 6.0 to 10.0. Results supported the use of vitamin K as an effective treatment option for the reversal of excessive anticoagulation in patients receiving warfarin therapy.
- In their 2008 guidelines for the management of vitamin K antagonists, the American College of Chest Physicians makes the following recommendations for the management of nontherapeutic INRs:
o For patients with an INR above the therapeutic range but <5.0 with no significant bleeding, the dosage of warfarin should be lowered or a dose omitted. In addition, more frequent monitoring is recommended. Therapy can be resumed at an appropriately adjusted dose when the INR is at a therapeutic level. If only minimally above therapeutic range or associated with a transient causative factor, no dose reduction may be required.

o For patients with an INR ≥5.0 to <9.0 and no significant bleeding, one or two doses of warfarin should be omitted and the patient should be monitored more frequently. Therapy can be resumed at an appropriately adjusted dose when the INR is at a therapeutic level.

o For patients with an INR ≥5.0 to <9.0 and no significant bleeding, it is suggested that a dose of warfarin is omitted and vitamin K (1 to 2.5 mg) is administered orally, particularly if the patient is at an increased risk of bleeding. If more rapid reversal is required because the patient requires surgery, it is suggested to administer vitamin K (≤5 mg) orally, with the expectation that an INR reduction will occur in 24 hours. If at that point the INR is still high, additional vitamin K (1 to 2 mg) administered orally is suggested.

o For patients with an INR ≥9.0 and no significant bleeding, warfarin therapy should be held and a higher dose of vitamin K (2.5 to 5 mg) should be administered orally, with the expectation that the INR will be reduced substantially in 24 to 48 hours. Clinicians should monitor the INR more frequently, administer additional vitamin K orally if necessary and resume therapy at an appropriately adjusted dose when the INR reaches the therapeutic range.

RECOMMENDATION
Phytonadione is a synthetic formulation of the endogenous form of vitamin K1 which is indicated in anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives and hypoprothrombinemia secondary to antibacterial therapy, administration of salicylates, obstructive jaundice or biliary fistulas. Clinical trial evidence demonstrating the safety and efficacy of vitamin K is limited; however, it is an established therapy in correcting excessive anticoagulation from warfarin and recognized by current clinical guidelines. The American College of Chest Physicians recommends oral vitamin K should be administered to patients with an INR ≥5.0 to <9.0, especially in patients at increased risk of bleeding, and for patients with an INR ≥9.0 regardless of bleeding risk. As it is the only oral vitamin K product currently available, it is recommended phytonadione should be available.

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RE-REVIEW: VITAMIN K

References
6. Ageno W, Garcia D, Silingardi M, Galli M, Crowther M. A randomized trial comparing 1 mg

RE-REVIEW: VITAMIN D & VITAMIN D ANALOGS

BACKGROUND

- Included in this review are the naturally occurring (calcitriol and ergocalciferol) and synthetic forms (doxercalciferol and paricalcitol) of vitamin D available by prescription.
- The biological actions of these agents are mediated through binding of the vitamin D receptor, which results in the selective activation of vitamin D responsive pathways. Vitamin D receptors are found in the parathyroid gland, intestine, kidney and bone and work to maintain parathyroid function and calcium and phosphorus homeostasis.
- All of the vitamin D and vitamin D analog products, with the exception of ergocalciferol, are FDA approved for the management of hyperparathyroidism associated with chronic kidney disease (CKD). Ergocalciferol is the only product FDA approved for the treatment of familial hypophosphatemia and refractory rickets. In addition, ergocalciferol is indicated for the management of hypoparathyroidism, as is calcitriol.
- Adverse effects associated with the vitamin D and vitamin D analog products are, in general, similar to those associated with excessive vitamin D intake (i.e., hypercalcemia syndrome or calcium intoxication). In addition to hypercalcemia, excessive administration of vitamin D compounds can cause over suppression of parathyroid hormone (PTH), hypercalciuria, hyperphosphatemia and adynamic bone disease.
  - The vitamin D/vitamin D analog products are contraindicated in patients with hypercalcemia or evidence of vitamin D toxicity.
  - Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures.
  - Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. Oral calcium-based or other non-aluminum-containing phosphate binders and a low phosphate diet should be used to control phosphorus levels in patients with CKD. As the most active, naturally occurring vitamin D derivative in humans, the effects of calcitriol often induce hypercalcemia and renal stones, and exacerbate hyperphosphatemia in patients with CKD. These limitations led to the development of synthetic calcitriol analogs that retain the ability to suppress PTH gene expression and levels, but with lower calcemic and phosphatemic side effects.
  - Magnesium-containing preparations (e.g., antacids) should not be used concomitantly with calcitriol or doxercalciferol in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.
- In general, the evaluation of these agents has focused on maintaining levels of parathyroid hormone (PTH) and calcium within predetermined target ranges, or gauged by bone histomorphometry. As an established treatment, head-to-head trials would allow for comparisons among the available products; however, few exist. Demonstration of differences among these products is inherently difficult, particularly when drugs such as calcium-based phosphate binders are used concomitantly.
According to guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) work group, abnormalities in phosphorus, calcium and vitamin D should be evaluated for and corrected in patients with CKD Stages 3 to 5 with intact PTH levels above the upper limit of normal for the assay being used. If a patient’s PTH level progressively rises and remains above the upper limit of normal for the assay despite correction of modifiable factors, calcitriol and vitamin D analog products or calcimimetics should be added to the patients therapy. Specifically, calcitriol or vitamin D analog products are recommended for patients with CKD Stage 3 to 5 not yet on dialysis, and calcitriol or vitamin D analog products, calcimimetics or a combination of the two are recommended in patients with CKD Stage 5D. The KDIGO guidelines do not recommend the use of one vitamin D/vitamin D analog product over another.

For patients with CKD Stages 3 and 4, the Kidney Disease Outcomes Quality Initiative guidelines recommend treatment with an active vitamin D sterol when serum levels of 25(OH)-vitamin D are ≥30 ng/mL and intact PTH levels are above the target range for the CKD Stage. Patients with CKD on dialysis with intact PTH levels >300 pg/mL, should also receive treatment with an active vitamin D sterol. The K/DOQI guidelines do not recommend the use of one vitamin D/vitamin D analog product over another. The K/DOQI also suggests the use of ergocalciferol for the prevention and treatment of vitamin D insufficiency and vitamin D deficiency in CKD patients.

RECOMMENDATION
All of the vitamin D and vitamin D analog products, with the exception of ergocalciferol, are FDA approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. Ergocalciferol is the only product FDA approved for the treatment of familial hypophosphatemia and refractory rickets. Ergocalciferol and calcitriol are also indicated for the management of hypoparathyroidism. According to current guidelines from the National Kidney Foundation, vitamin D/vitamin D analog products are appropriate for patients with CKD Stages 3 to 5, and in whom PTH is progressively rising and remains persistently above the upper limit of normal for the assay. Head-to-head clinical trials comparing the individual vitamin D/vitamin D analog products are limited and current guidelines do not differentiate between the available agents in this class. However, calcitriol often induces adverse effects such as hypercalcemia, renal stones, and exacerbations of hyperphosphatemia. Synthetic vitamin D analogs, such as doxercalciferol and paricalcitol, have been developed to achieve the same suppression of PTH levels with limited calcemic and phosphatemic side effects. It is recommended at least two vitamin D/vitamin D analog products be available for use, one of which should be ergocalciferol due to its unique indications. Additionally, due to the relative lower incidence of hypercalcemia and hyperphosphatemia associated with the synthetic vitamin D analogs, at least one synthetic vitamin D analog should be available for patients with a history of these adverse events with calcitriol.

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Clinical Criteria for Hectorol® & Zemplar®
Hectorol® or Zemplar® will be approved for recipients experiencing (or with a history of) hypercalcemia and/or hyperphosphatemia with calcitriol use.
COMMITTEE VOTE:

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References

RE-REVIEW: PRENATAL VITAMINS

BACKGROUND

- A wide variety of prenatal vitamins are currently available including both prescription and OTC products. Most vitamins contain folic acid and iron in varying amounts, in addition to other vitamins and minerals. Some preparations contain additional ingredients including omega-3 fatty acids, docusate, and L-methylfolate.
- Prenatal vitamins are indicated to improve the nutritional status of women prior to conception, throughout pregnancy and during the post-natal period in lactating and non-lactating mothers.
- Adverse drug events associated with prenatal vitamins include abdominal pain, constipation, dark stools, diarrhea, nausea, and vomiting.
  - Prenatal vitamins containing iron carry a black box warning regarding the potential of accidental overdose of iron-containing products as a leading cause of fatal poisoning in children under six years of age.
  - Ingestion of more than 3 g/day of omega-3 fatty acids has been shown to have potential antithrombotic effects, including increased bleeding time and INR. Administration should be avoided in patients on anticoagulants and those known to have an inherited or acquired bleeding diathesis.
  - FOLates may obscure pernicious anemia in that hematologic remission may occur while neurologic manifestations remain progressive. Iron supplementation should not be used in patients with hemochromatosis and hemosiderosis
  - No clinically significant drug interactions with the prenatal vitamins were identified in the clinical literature; however, since many prenatal vitamins contain iron, drug interactions expected to occur with iron containing products may also occur with prenatal vitamins containing iron.
- Recent attention has been paid to the use of omega-3 fatty acid supplementation and subsequent effects on pregnancy outcomes, birth weight and visual and neurocognitive developments. In general, meta-analyses evaluating the effects of omega-3 fatty acids on pregnancy and infant/child outcomes have not demonstrated significant results and the effects of supplementation on child development also remain uncertain. More studies are needed to adequately evaluate the place of omega-3 fatty acids in this population of patients.
A meta-analysis was conducted which contained results from 89 randomized controlled trials to determine the effect of omega-3 fatty acid supplementation in pregnant and breastfeeding women and infants. No significant association was observed with supplementation and the duration of gestation, incidence of eclampsia, preeclampsia, and gestational hypertension, incidence of SGA, growth, neurocognitive development or visual function.

- Current guidelines recommend that women of reproductive age should maintain a healthy lifestyle and consume a well-balanced diet to optimize maternal health and reduce the risk of birth defects, perinatal morbidity and chronic health problems in their children. Professional organizations, including the United States Preventative Task Force, the American College of Obstetricians and Gynecologists, the National Institute for Health and Clinical Excellence and the American Academy of Family Physicians, agree on the importance of supplemental folic acid in pregnant women and those of child-bearing age and generally recommend 400 to 800 µg of folic acid daily. The Centers for Disease Control and Prevention recommends 27 mg/day of iron for all pregnant women, though higher amounts are required in patients with iron deficiency anemia.

RECOMMENDATION
Prenatal vitamins are available both over-the-counter and by prescription and differ based on the amount of nutrients contained in the various preparations. All of the available prenatal vitamins are indicated to improve the nutritional status of women prior to conception, throughout pregnancy and during the post-natal period in lactating and non-lactating mothers. Professional organizations agree on the importance of supplemental folic acid in pregnant women and those of child-bearing age and generally recommend 400 to 800 µg of folic acid daily to prevent neural tube defects. There are no head-to-head trials comparing agents in this class and none of the available guidelines differentiate between any of the available agents in this class. Meta-analyses evaluating the effects of omega-3 fatty acids on pregnancy and infant/child outcomes have not demonstrated significant results and the effects of supplementation on child development also remain uncertain. In order to ensure patient and provider choice, it is recommended at least five prenatal vitamins should be available for use in females of child-bearing age.

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### RE-REVIEW: PRENATAL VITAMINS

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**Clinical Criteria for chewables:**
- Will be approved if patient is unable to swallow tablets

**COMMITTEE VOTE:**

- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION
REFERENCES

RE-REVIEW: FOLIC ACID

BACKGROUND
- This class review encompasses the available prescription folic acid products and folic acid derivatives.
- Folic acid is a B complex vitamin and is the synthetic form of folate. L-methylfolate is the biologically active form of folate found in the circulation. Folic acid must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to L-methylfolate, which is then transported across cell membranes by receptor-mediated endocytosis. L-methylfolate readily crosses the blood brain barrier where it modulates the formation of the monoamines serotonin, norepinephrine, and dopamine. Having defective or less functional forms of any of the enzymes necessary for the conversion of folic acid could result in inadequate concentrations of levomefolate in the central nervous system.
- Folic acid is FDA approved for the treatment of megaloblastic anemias due to a deficiency of folic acid and in anemias of nutritional origin, pregnancy, infancy, or childhood. Other agents included in this review are considered medical food/dietary supplements and contain folic acid, or a form of folic acid in addition to other vitamins. These agents are not reviewed by the FDA.
- Adverse events most commonly associated with the use of folic acid are gastrointestinal in nature, including anorexia, nausea, abdominal distention, flatulence and bitter/bad taste.
  - If folic acid is administered to a patient with undiagnosed anemia, there is risk of obscuring the diagnosis of pernicious anemia. This could lead to an alleviation of the hematologic manifestations of anemia while allowing neurological complications to progress.
  - Concomitant administration of folic acid with methotrexate, nitrofurantoin, primidone or barbiturates may result in decreased folate levels. Concomitant administration of folic acid and barbiturates, phenytoin or fosphenytoin may result in decreased levels and the need to adjust the anticonvulsant.
A Cochrane review evaluated four trials, with 6,425 women enrolled and found that supplementation with folic acid significantly reduced the risk of neural tube defects compared to placebo and multivitamins without folic acid. (RR, 0.28; 95% CI, 0.13 to 0.58).

Professional organizations, including the United States Preventative Task Force, the American College of Obstetricians and Gynecologists, the National Institute for Health and Clinical Excellence and the American Academy of Family Physicians, agree on the importance of supplemental folic acid in pregnant women and those of child-bearing age and generally recommend 400 to 800 µg of folic acid daily. The United States Department of Agriculture recommended daily amount of folic acid for males and females over 18 years of age is 400 µg daily and for pregnant and lactating women is 600 µg and 500 µg respectively.

**RECOMMENDATION**

Folic acid is a B complex vitamin and is the synthetic form of folate. Folic acid is FDA approved for the treatment of megaloblastic anemias due to a deficiency of folic acid and in anemias of nutritional origin, pregnancy, infancy, or childhood. L-methyfolate products are considered a medical food or dietary supplement and have not been reviewed by the FDA. Professional organizations agree on the importance of supplemental folic acid in pregnant women and those of child-bearing age and generally recommend 400 to 800 µg of folic acid daily to prevent neural tube defects. Since it is the only FDA-approved agent in this class, it is recommended at least folic acid be available for use.

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**Clinical Criteria for L-methylfolate (Deplin®)**

- Will be approved if patient has documented methylenetetrahydrofolate reductase (MTHFR) mutation / deficiency

**COMMITTEE VOTE:**

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**References**


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**RE-REVIEW: FLUORIDE**

**BACKGROUND**

- Dental caries, or tooth decay, is an infectious, multifactorial disease that results from an overgrowth of organisms that are part of normally occurring human dental flora. It has been reported that dental caries may be the most prevalent infectious disease in children within the United States, and that in this patient population the decay of primary teeth can affect growth, lead to malocclusion and result in significant pain and potentially life-threatening swelling. The relationship between fluoride and dental caries was first noted in the early 20th century and the ability of fluoride to inhibit or reverse the initiation and progression of dental caries is well documented. This class review will focus on the currently available prescription fluoride products for outpatient use.

- Fluoride is known to control dental caries in several ways. When present in the mouth, fluoride is retained and concentrated in plaque. Fluoride inhibits the demineralization of sound enamel and enhances the recovery of demineralized enamel resulting in an improved enamel crystal structure. In addition, fluoride also prevents dental caries by affecting the activity of the cariogenic bacteria. Laboratory and epidemiologic research has established that the predominant method by which fluoride prevents dental caries is via topical administration.

- Fluoride is FDA-approved for the prevention of dental caries.

- Adverse drug events, with less than a one percent incidence, associated with sodium fluoride include discoloration of teeth, rash, nausea and vomiting.
  - Different sources suggest different levels of water fluoridation as a contraindication for the use of sodium fluoride. One source notes that sodium fluoride is contraindicated when fluoride content of drinking water is >0.7 parts per million (ppm), while another states >0.6 ppm. Sodium fluoride 1 mg tablets should not be used in children less than three years of age or when drinking water fluoride content is ≥0.3 ppm.
  - Prolonged ingestion of fluoride with excessive doses may result in dental fluorosis and osseous changes; therefore, the recommended dosage of sodium fluoride should not be exceeded.
  - There are no known significant drug interactions associated with sodium fluoride documented in the clinical literature.

- Much of the research on the effectiveness of individual fluoride products in the prevention and control of dental caries was conducted before 1980, when dental caries were more common and severe. Due to the age, quality and abundance of clinical trial data, systematic and Cochrane reviews that have been published regarding the use of fluoride supplementation are summarized below.
A Cochrane review evaluated the use of one topical fluoride product (toothpastes, mouthrinses, gels or varnishes) compared to another for the prevention of dental caries in children and adolescents. Results from this review demonstrate that fluoride toothpastes, mouthrinses and gels reduce tooth decay to a similar extent; however, toothpaste is more likely to be regularly used. In addition, no strong evidence was found to support that fluoride varnishes are more effective than other topical fluoride products. There were 17 trials included in this review; the majority of which published between 1965 and 1987, with two published in 1991 and 1995, respectively.

A Cochrane review evaluated the use of combination topical fluoride products (toothpastes, mouthrinses, gels or varnishes) compared to monotherapy with any topical fluoride product for the prevention of dental caries in children and adolescents. Results demonstrate that additional forms of topical fluoride to fluoride toothpaste can reduce tooth decay more than fluoride toothpaste alone, but the additional benefit is not substantial. There were 12 trials included in this review; all of which were published between 1970 and 1988.

In a systematic review of fluoride supplementation and dental caries commissioned by the American Dental Association Council on Scientific Affairs, it was concluded that there is weak and inconsistent evidence that the use of fluoride supplements (tablets, lozenges or drops) prevents dental caries in primary teeth; however, the evidence supports the use of fluoride supplementation for the prevention of dental caries in permanent teeth. There were 12 trials included in this review; the majority of which were published between 1968 and 1989, with one published in 1998.

- Water fluoridation for the prevention of dental caries has been endorsed by over 90 professional health organizations as the most effective dental public health measure in existence. In addition to water fluoridation, guidelines from the American Dental Association (ADA) state that all patients, regardless of age or risk group, should use an appropriate amount of fluoride toothpaste when brushing twice daily. For patients at low risk of dental caries, the ADA states fluoridated water and fluoride toothpastes may provide adequate dental caries prevention. For patients at moderate or high risk of dental caries, the ADA as well as the Centers for Disease Control and Prevention (CDC) state additional preventative interventions should be considered, including use of additional fluoride products at home. Populations believed to be at increased risk for dental caries are those with low socioeconomic status or low levels of parental education, those who do not seek regular dental care and those without dental insurance or access to dental services. Individual factors that possibly increase risk include active dental caries; history of high dental caries experience in older siblings or caregivers; root surfaces exposed by gingival recession; high levels of infection with cariogenic bacteria; impaired ability to maintain oral hygiene; malformed enamel or dentin; reduced saliva flow because of medications, radiation treatment or disease; low salivary buffering capacity and the wearing of space maintainers, orthodontic appliances or dental prostheses.

- The Committee of Nutrition of the American Academy of Pediatrics released an interim policy recommendation on fluoride supplementation in 1995 in response to an increased incidence of dental fluorosis in children living in the United States. In this recommendation, fluoride supplementation is no longer recommended from birth, and recommended doses have been decreased during the first six years of life. Additionally, the level of water fluoride content when supplements are not needed has been lowered from 0.7 to 0.6 parts per million.
RECOMMENDATION
The benefits of fluoride supplementation for dental caries prevention are well established. The success in reducing dental caries observed after the implementation of water fluoridation in 1945, lead to the production of several fluoride-containing products, which are FDA-approved for the prevention of dental caries. Historically, the benefits of fluoride were believed to be via systemic administration; however, now it is recognized that the primary mode of action of fluoride for the prevention of dental caries is topical. Consensus guidelines from the ADA and CDC state that patients at low risk for dental caries may receive adequate fluoride supplementation via fluoridated water and fluoride-containing toothpaste. However, patients at a higher risk for dental caries, including patients receiving head and neck radiation, may benefit from additional topical fluoride supplementation. Due to the fact that only topical fluoride products are recommended in the current guidelines, topical fluoride products can be considered the superior products in this class. Therefore, it is recommended that at least two topical fluoride products should be available for use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: FLUORIDE

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RE-REVIEW: MULTIVITAMINS WITH FLUORIDE

BACKGROUND

- Vitamins are typically categorized as dietary supplements and are thought to improve health when taken in small amounts as alternatives or supplements to drugs. Major vitamins are available for administration as single-entity supplements; however, multivitamins which contain at least one Recommended Daily Allowance of all major vitamins are also available. Some multivitamins also contain minerals such as fluoride. This class review will focus on the currently available prescription multivitamins with fluoride. Please note, agents in this class are only covered for TennCare recipients under the age of 21 years old.

- Fluoride is known to control dental caries in several ways. When present in the mouth, fluoride is retained and concentrated in plaque. Fluoride inhibits the demineralization of sound enamel and enhances the recovery of demineralized enamel resulting in an improved enamel crystal structure. In addition, fluoride also prevents dental caries by affecting the activity of the cariogenic bacteria. Laboratory and epidemiologic research has established that the predominant method by which fluoride prevents dental caries is via topical administration.

- Multivitamins plus fluoride are a well established dietary supplement used for the prevention and/or treatment of vitamin and mineral deficiencies. Fluoride, specifically, has demonstrated effectiveness in preventing dental caries. Please note that the multivitamins plus fluoride products are labeled for over the counter use and are considered a dietary supplement. Currently dietary supplements do not require Food and Drug Administration approval as they are handled differently than over the counter and prescription drugs.

- No specific adverse events for the multivitamins plus fluoride were identified in the clinical literature. However, fluoride is associated with discoloration of teeth, rash, nausea and vomiting.
  - No specific contraindications/precautions for the multivitamins plus fluoride were identified in the clinical literature.
  - No clinically significant drug interactions with the multivitamins plus fluoride were identified in the clinical literature.

- In a systematic review comparing fluoride tablets, lozenges or drops with no exposure to any source of systemic fluoride in children, three reports regarding the effectiveness of fluoride supplements with added vitamins were discussed.
  - In one, children who started fluoride supplementation with added vitamins from birth to three years, had a significantly lower mean number of decayed, extracted because of dental caries and filled surfaces of primary teeth compared to children who received only vitamin supplements ($P<0.001$).
  - Dental caries were also reduced among children who received vitamin drops containing 0.5 mg fluoride starting at the age of two to three weeks until the age of six years. It was also been reported that fluoride supplementation with either fluoride drops until the age of three years followed by chewable tablets or vitamin/fluoride tablets for a duration of seven years is effective in reducing dental caries in primary teeth.
Overall, this review concluded that there is weak and inconsistent evidence that the use of fluoride supplements (tablets, lozenges or drops) prevents dental caries in primary teeth; however, the evidence supports the use of fluoride supplementation for the prevention of dental caries in permanent teeth. There were 12 trials included in this review; the majority of which were published between 1968 and 1989, with one published in 1998.

- Water fluoridation for the prevention of dental caries has been endorsed by over 90 professional health organizations as the most effective dental public health measure in existence. In addition to water fluoridation, guidelines from the American Dental Association (ADA) state that all patients, regardless of age or risk group, should use an appropriate amount of fluoride toothpaste when brushing twice daily. For patients at low risk of dental caries, the ADA states fluoridated water and fluoride toothpastes may provide adequate dental caries prevention. For patients at moderate or high risk of dental caries, the ADA as well as the Centers for Disease Control and Prevention (CDC) state additional preventative interventions should be considered, including use of additional fluoride products at home. Populations believed to be at increased risk for dental caries are those with low socioeconomic status or low levels of parental education, those who do not seek regular dental care and those without dental insurance or access to dental services. Individual factors that possibly increase risk include active dental caries; history of high dental caries experience in older siblings or caregivers; root surfaces exposed by gingival recession; high levels of infection with cariogenic bacteria; impaired ability to maintain oral hygiene; malformed enamel or dentin; reduced salivary flow because of medications, radiation treatment or disease; low salivary buffering capacity and the wearing of space maintainers, orthodontic appliances or dental prostheses.

- The Committee of Nutrition of the American Academy of Pediatrics released an interim policy recommendation on fluoride supplementation in 1995 in response to an increased incidence of dental fluorosis in children living in the United States. In this recommendation, fluoride supplementation is no longer recommended from birth, and recommended doses have been decreased during the first six years of life. Additionally, the level of water fluoride content when supplements are not needed has been lowered from 0.7 to 0.6 parts per million.

- The use of multivitamins plus fluoride products are not specifically addressed among the available guidelines; however, if based on individual characteristics and fluoride requirements, the amount of fluoride contained within a multivitamin plus fluoride product is appropriate, these products may be considered as an alternative to single entity fluoride products.

RECOMMENDATION

Multivitamins plus fluoride are a well established dietary supplement used for the prevention and/or treatment of vitamin and mineral deficiencies. Fluoride, specifically, has demonstrated effectiveness in preventing dental caries. Consensus guidelines from the ADA and CDC state that patients at low risk for dental caries may receive adequate fluoride supplementation via fluoridated water and fluoride-containing toothpaste. However, patients at a higher risk for dental caries may benefit from additional topical fluoride supplementation. The use of multivitamins plus fluoride products are not specifically addressed among the available guidelines; however, if, based on individual characteristics and fluoride requirements, the amount of fluoride contained within a multivitamin plus fluoride product is appropriate, then these products may be considered as an alternative to single entity fluoride products. Therefore, it is recommended at least one liquid and one chewable multivitamin with fluoride product should be available for use.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION
# RE-REVIEW: MULTIVITAMINS WITH FLUORIDE

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## References

# RE-REVIEW: MULTIVITAMINS WITH IRON

## BACKGROUND
- Vitamins are typically categorized as dietary supplements and are thought to improve health when taken in small amounts as alternatives or supplements to drugs. Major vitamins are available for administration as single-entity supplements; however, multivitamins which contain at least one Recommended Daily Allowance of all major vitamins are also available. Some multivitamins also contain minerals such as iron. This class review will focus on the currently available prescription and OTC multivitamins with iron. Please note, agents in this class are only covered for TennCare recipients under the age of 21 years old.
- Multivitamins plus iron are a well established dietary supplement used for the prevention and/or treatment of vitamin and mineral deficiencies. Please note that the multivitamins plus iron products are labeled for over the counter use and are considered a dietary supplement. Currently, dietary supplements do not require FDA approval.
- No specific adverse events for the multivitamins plus iron were identified in the clinical literature. However, there is a potential for adverse events associated with the individual products as the administration of iron is commonly associated with gastrointestinal discomfort, nausea, constipation or diarrhea, and stools may appear darker in color.
  - Severe iron toxicity may occur in overdosage with multivitamins plus iron products, especially in children. Iron is a leading cause of fatal poisoning in children; therefore, all products containing iron should be stored out of reach of children in child-resistant containers.
  - No clinically significant drug interactions with the multivitamins plus iron were identified in the clinical literature; however, since these products contain iron, drug interactions expected to occur with iron containing products may also occur with multivitamins containing iron.
- Two trials compared the use of multivitamins with iron to the use of multivitamins without iron in patients between age 5 and 7 months of age. While one trial found a difference in the proportion of patients with anemia (11% vs 19%), the second trial found no statistically significant differences in any hematologic outcomes between the two treatment groups.
According to the most current guidelines from the American Academy of Pediatrics regarding the prevention of iron deficiency and iron deficiency anemia in infants and young children, healthy, term infants who are exclusively or partially breastfed should start receiving oral iron supplementation starting at four months of age. Supplementation in these patients should be continued until iron-containing complementary foods can be introduced into their diet. Preterm, breastfed infants require an oral iron supplement by one month of age, which is to be continued until they are started on an iron-fortified formula or begin eating iron-containing complementary foods. Liquid iron supplements are appropriate in infants ages six to 12 months of age if the iron needs are not being met by their current diet. Similar to infants, if iron needs are not met through the diet; liquid iron supplements are suitable for children 12 to 36 months of age, and chewable multivitamins can be used for children three years of age or older.

The use of multivitamins plus iron products is not consistently addressed among the available guidelines; however, if based on individual patient characteristics and iron requirements, the amount of iron contained within a multivitamin plus iron product is appropriate, these products may be considered as an alternative to single entity iron products.

RECOMMENDATION
Multivitamins plus iron are a well established dietary supplement used for the prevention and/or treatment of vitamin and mineral deficiencies. Current guidelines from the American Academy of Pediatrics recommend breastfed preterm infants should start receiving oral iron supplementation by one month of age and breastfed term infants start receiving oral iron supplementation at four months of age. Iron supplementation should continue until iron needs are being met by the patient’s diet. If the iron needs are not being met by the patient’s diet, liquid iron supplements are suitable for children up to 36 months of age, and chewable multivitamins can be used for children three years of age or older. The use of multivitamins plus iron products is not consistently addressed among the available guidelines; however, the amount of iron contained within a multivitamin plus iron product may be appropriate to fulfill a patient’s iron needs and these products may be considered as an alternative to single entity iron products in some patients. Therefore, it is recommended at least four multivitamin with iron products should be available for use, which should contain at least one liquid and one chewable formulation.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

RE-REVIEW: MULTIVITAMINS WITH IRON

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References

Clinical Criteria for Cymbalta

Cymbalta will be authorized for the following diagnoses:

- Depression/Major Depressive Disorder/Generalized Anxiety Disorder: Approval after trial and failure of one SSRI AND one preferred SNRI
- Diabetic peripheral neuropathic pain: Approved without trial and failure of an SSRI or any preferred agents within the SNRI class.
- Fibromyalgia: Approval will be granted after trial and failure, contraindication, or intolerance to:
  - A tricyclic antidepressant or skeletal muscle relaxant, AND
  - At least ONE of the following: SSRI, a preferred SNRI, pregabalin, or gabapentin
- **Chronic musculoskeletal pain:** Approval after at least TWO week trial and failure of, or intolerance or contraindication to, ALL of the following:
  - Acetaminophen; AND
  - One NSAID; AND
  - Tramadol, OR preferred opiate analgesic

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Clinical Criteria for Butrans®

Approval will be authorized for recipients meeting ALL of the following criteria:

- Diagnosis of moderate to severe pain with need for around-the-clock analgesia for an extended period, AND
- Have tried and failed or have a contraindication, drug to drug interaction, or history of unacceptable side effects with, at least **TWO** preferred long-acting narcotics, OR the recipient is unable to swallow or absorb oral medications, AND
- The prescriber has checked the Tennessee Controlled Substance database within the last 30 days.

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