

Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Topical Immunomodulators

Overview:

Atopic dermatitis, the most common form of eczema, affects about 35 million people in the United States. This disease can occur at any age, but first appears most often in infants and young children. In atopic dermatitis, the skin becomes extremely itchy. Scratching leads to redness, swelling, cracking, “weeping” clear fluid, and finally, crusting and scaling. Although the cause of atopic dermatitis is unknown, certain events such as changes in temperature or humidity, chemical irritants, physical irritants, allergies, intense emotion or stress, and infections may cause “flare-ups”. A flare-up occurs when the immune system in the skin overreacts to environmental or emotional triggers and causes symptoms such as an itchy rash to appear. Pimecrolimus (Elidel[®]) and tacrolimus (Protopic[®]) belong to a therapeutic class called topical immunomodulators. These are pharmacological options that can significantly contribute to inflammatory relief.

In the past, topical corticosteroids were the mainstay for treating eczema. However, a number of side effects including thinning of the skin, formation of dilated blood vessels, and infection have been reported. The topical immunomodulators provide eczema patients with a steroid-free alternative to traditional therapies without the common side effects. When applied topically, these therapies produce powerful anti-inflammatory effects on the skin without interfering with the body’s immune system. The mechanism of action of both pimecrolimus and tacrolimus in atopic dermatitis is unknown. However, it has been demonstrated that pimecrolimus binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium dependent phosphatase, calcineurin. As a result, it inhibits T-cell activation by blocking the transcription of early cytokines. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE. Tacrolimus has been demonstrated to inhibit T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils. The most common

adverse event associated with both pimecrolimus and tacrolimus is application site skin reactions.

Pimecrolimus was approved by the FDA in January 2002 and is available as a 1% cream in tubes of 30 grams, 60 grams, and 100 grams. Tacrolimus was approved by the FDA in December 2000 and is available as a 0.03% and 0.1% ointment in tubes of 30 grams, 60 grams, and 100 grams. On February 15, 2005, the FDA announced the addition of a Black Box warning to the professional labels for pimecrolimus and tacrolimus, instructing prescribers to use only after failure of other eczema treatments due to a possible increased cancer risk. Furthermore, the Black Box warning included language indicating calcineurin inhibitors are not indicated for use in children less than two years of age. A Medication Guide must now accompany all prescriptions for pimecrolimus and tacrolimus.

Generic Name	Brand Name	Manufacturer	Generic Available
Pimecrolimus	Elidel [®]	Novartis	N
Tacrolimus	Protopic [®]	Astellas	N

Summary:

Available data suggests that both agents are effective in treating atopic dermatitis. However, neither agent has proven to be significantly better than the other. The preferred drug list should be based upon FDA-approved indications, efficacy, and cost.