

Texas Vendor Drug Program

Drug Use Criteria: Topical Calcineurin Inhibitors – Pimecrolimus (Elidel®), Tacrolimus (Protopic®)

Publication History

1. Developed: October 2006
2. Revised: **January 2022**; November 2019; December 2017; August 2015; December 2013; February 2012; May 2010; December 2006.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

Prepared by:

- Drug Information Service, UT Health San Antonio.
- The College of Pharmacy, The University of Texas at Austin.



TEXAS
Health and Human
Services

*Medical and
Social Services*

1 Dosage

Topical calcineurin inhibitors are FDA-approved as second-line agents for atopic dermatitis management in non-immunocompromised adults and children greater than 2 years of age who have not responded to other available therapies for atopic dermatitis. Pimecrolimus (Elidel®) is indicated for short-term, intermittent treatment of mild-to-moderate atopic dermatitis, while tacrolimus (Protopic®) is indicated for short-term, intermittent therapy of moderate-to-severe atopic dermatitis.¹⁻⁴

Due to the uncertainty of the carcinogenic risk, the FDA issued a Black Box Warning for topical calcineurin inhibitors in 2006 stating that rare cases of malignancy have been reported, continuous long-term use should be avoided, and application should be limited to areas of the body with atopic dermatitis. Additionally, topical calcineurin inhibitors are not indicated for use in children less than 2 years of age.¹⁻⁶

1.1 Adults

Dosage recommendations for available calcineurin inhibitors are summarized in Table 1.

Table 1. Recommended Adult Dosages for Topical Calcineurin Inhibitors¹⁻⁴

Drug Name	Dosage Strength	Recommended Dose/Directions
pimecrolimus (Elidel®, generics) cream	1% - 30 g, 60g, 100 g tube	apply thin layer of cream to affected area twice daily until symptoms resolve; use should be confined only to areas affected by atopic dermatitis; should not be used with occlusive dressings

Drug Name	Dosage Strength	Recommended Dose/Directions
tacrolimus (Protopic®, generics) ointment	0.03% - 30 g, 60 g, 100 g tube	apply thin layer of 0.03% or 0.1% ointment to affected area twice daily, rubbing in completely, and continue until symptoms resolve; use should be confined only to areas affected by atopic dermatitis; should not be used with occlusive dressings
	0.1% - 30 g, 60 g, 100 g tube	

Patient profiles documenting prescriptions for greater than the equivalent of one 60 g tube of pimecrolimus cream or tacrolimus ointment per 30-day time period will be reviewed.

1.2 Pediatrics

A Black Box Warning states that the long-term safety of topical calcineurin inhibitors has not been established, and continuous long-term use is not recommended. While a causal relationship for the incidence of malignancy has not been established, topical calcineurin inhibitor use should be avoided in children younger than 2 years of age as the effect on the developing immune system is not known.¹⁻⁶

Recommended pediatric dosages for topical calcineurin inhibitors are summarized in Table 2.

Table 2. Recommended Pediatric Dosages for Topical Calcineurin Inhibitors¹⁻⁴

Drug Name/Strength	Recommended Dose/Directions
pimecrolimus 1% cream	<i>Children > 2 years of age:</i> apply thin layer of cream to affected area twice daily until symptoms resolve; use should be confined only to areas affected by atopic dermatitis; should not be used with occlusive dressings

Drug Name/Strength	Recommended Dose/Directions
tacrolimus 0.03% ointment	<i>Children 2-15 years of age: use only 0.03% strength; apply thin layer of ointment to affected layer twice daily, rubbing in completely, and continue until symptoms resolve; use should be confined only to areas affected by atopic dermatitis; should not be used with occlusive dressings</i>
0.03% or 0.1% ointment	<i>Children 15-17 years of age: apply thin layer of 0.03% or 0.1% ointment to affected area twice daily, rubbing in completely, and continue until symptoms resolve; use should be confined only to areas affected by atopic dermatitis; should not be used with occlusive dressings</i>

2 Duration of Therapy

Continuous, long-term use of topical calcineurin inhibitors should be avoided, and use should be confined only to areas affected by atopic dermatitis. Patients whose symptoms do not resolve following six weeks of calcineurin inhibitor therapy should be re-evaluated by their health care provider to confirm the diagnosis of atopic dermatitis.¹⁻⁴

Patients with a confirmed diagnosis of atopic dermatitis will require chronic, intermittent therapy for this condition. Patient profiles with either excessive prescriptions for calcineurin inhibitors during a 30-day time period (> 1 x 60 g tube) or without a definitive diagnosis of atopic dermatitis while prescribed a topical calcineurin inhibitor during a 90-day time period will be reviewed.

3 Duplicative Therapy

Concurrent administration of two or more topical calcineurin inhibitors does not provide enhanced therapeutic benefit and may result in additive adverse effects. Concurrent administration of pimecrolimus cream and tacrolimus ointment is not recommended and will be reviewed.

4 References

1. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedexsolutions.com.libproxy.uthscsa.edu/>. **Accessed December 9th, 2021.**
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: <http://www.clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/>. **Accessed December 9th, 2021.**
3. Pimecrolimus (Elidel®) package insert. Valeant -Bausch Health, **September 2020.**
4. Tacrolimus (Protopic®) package insert. Leo Pharma Inc., **April 2019.**
5. U.S. Department of Health and Human Services. U.S. Food and Drug Administration. FDA approves updated labeling with boxed warning and medication guide for two eczema drugs, Elidel and Protopic. (January 19, 2006) Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm153941.htm>. **Accessed December 13th, 2021.**
6. **Ring, Johannes, et al. "The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy." Drug Safety, vol. 31, no. 3, Mar. 2008, pp. 185+. Gale OneFile: Health and Medicine, link.gale.com/apps/doc/A200506441/HRCA?u=txshracd2607&sid=bookmark-HRCA&xid=2bbaeb0b. Accessed 13 Dec. 2021.**

Additional Uncited Resources

Arellano FM, Wentworth CE, Arana A, et al. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol. 2007;127(4):808-16.

Asgari MM, Tsai A, Avalos L, Sokil M, Quesenberry CP. Association between topical calcineurin inhibitor use and keratinocyte carcinoma risk among adults with atopic dermatitis. JAMA Dermatol. 2020;156(10):1066–1073.

Berger TG, Duvic M, Van Voorhees AS, Frieden IJ. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. J Am Acad Dermatol. 2006;54:818-23.

Hui RL, Lide W, Chan J, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. Ann Pharmacother. 2009;43(12):1956-63.

Kalavala M, Dohil MA. Calcineurin inhibitors in pediatric atopic dermatitis. A review of current evidence. Am J Clin Dermatol. 2011;12(1):15-24.

Kang S, Lucky AW, Pariser D, et al, and the Tacrolimus Ointment Study Group. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol. 2001;44(Suppl1):S58-64.

Lam M, Zhu JW, Tadrous M, Drucker AM. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. JAMA Dermatol. 2021;157(5):549–558.

Langley RG, Eichenfield LF, Lucky AW, et al. Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. Pediatr Dermatol. 2008;25(3):301-7.

Luger TA, Lahfa M, Folster-Holst R, et al. Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. J Dermatolog Treat. 2004;15:169-78.

Paller AS, Fölster-Holst R, Chen SC, et al. No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. J Am Acad Dermatol. 2020;83(2):375-381.

Paller AS, Eichenfield LF, Kirsner RS, et al for the US Tacrolimus Ointment Study Group. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. Pediatrics. 2008;122(6):e1210-8.

Papp K, Staab D, Harper J, et al. Effect of pimecrolimus cream 1% on the long-term course of pediatric atopic dermatitis. Int J Dermatol. 2004;43:978-83.

Ruer-Mulard M, Aberer W, Gunstone A, et al. Twice-daily versus once-daily applications of pimecrolimus cream 1% for the prevention of disease relapse in pediatric patients with atopic dermatitis. Pediatr Dermatol. 2009;26(5):551-8.

Qureshi AA, Fischer MA. Topical calcineurin inhibitors for atopic dermatitis: balancing clinical benefit and possible risks. Arch Dermatol. 2006;142:633-7.

Reitamo S, Wollenberg A, Schopf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. Arch Dermatol. 2000;136:999-1006.

Reitamo S, Van Leent EJ, Ho V, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. J Allergy Clin Immunol. 2002;109:539-46.

Reitamo S, Harper J, Bos JD, et al. 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. Br J Dermatol. 2004;150:554-62.

Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. Pediatrics. 2015;135(4):597-606.

Thaci D, Salgo R Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. Clin Dermatol. 2010;28(1):52-6.

Trammell S, Shakil A, Wilder L, Daugird A. Clinical inquiries. What is the role of tacrolimus and pimecrolimus in atopic dermatitis? J Fam Pract. 2005;54:714-6.