# Topical Tacrolimus/Pimecrolimus Therapeutic Cheat Sheet

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## TRADE NAME[4,5]

- PROTOPIC® (tacrolimus 0.03% and 0.1% ointments)
- ELIDEL® (pimecrolimus 1% cream)

## MECHANISM OF ACTION[4,5]

- Both tacrolimus and pimecrolimus inhibit T-lymphocyte activation by binding to complex FKBP-12, which inhibits the downstream phosphatase activity of calcineurin. This prevents the translocation of nuclear factor of activated T cells (NF-AT), responsible for gene transcription of several lymphokines including IL-2 and Interferon gamma.
- Inhibit the transcription for genes which encode IL-3, IL-4, IL-5, IL-10, GM-CSF, and TNF-α, all involved in early stages of T-cell activation.
- Inhibit the release of pre-formed mediators from mast cells and basophils in the skin
- Tacrolimus also down regulates the expression of FcεRI on Langerhans cells.

## FDA-APPROVED FOR[4,5]

- *Second*-line therapy for the short-term and non-continuous chronic treatment of mild to moderate (pimecrolimus) and moderate to severe (tacrolimus) atopic dermatitis
- Tacrolimus 0.1%: approved for ages 16+
- Tacrolimus 0.03%: approved for ages 2+
- Pimecrolimus 1%: approved for ages 2+

## OFF-LABEL DERMATOLOGIC USES[6]

- Steroid-sparing alternative for numerous inflammatory and autoimmune skin conditions including:
  - Psoriasis
  - Seborrheic dermatitis
  - Vitiligo
  - Contact Dermatitis
  - Lichen planus
  - Lichen sclerosis
  - Morphea
  - Cutaneous lupus erythematosus

## DOSING

- Apply a thin layer to the affected skin twice daily

## ADMINISTRATION CONSIDERATIONS

- Product can be refrigerated to minimize “burning” side effect
- Moisturizers can be applied after use
- Use under occlusive dressings has not been studied
- may necessitate dose reduction or discontinuation.

## SIDE EFFECTS[4,5]

- The most common side effect is application site skin burning (stinging, soreness) and pruritus lasting minutes to hours
  - Mechanism: direct stimulation of sensory nerve fibers, leading to neuropeptide release (particularly substance P and calcitonin gene-related peptide (CGRP) which bind to and trigger mast cell degranulation7
  - Affects ~24% using Tacrolimus and 8-26% using pimecrolimus
  - Most common during the first few days of application and typically improves with repeated use
- Less common side effects:
  - Flu-like symptoms (28%)
  - Headache (11%)
  - Varicella zoster (mostly chicken pox) <5%
  - Vesicobullous rash <5%
  - Lymphadenopathy ~1%
- Pediatric use
  - Eczema herpeticum (0.5%)
  - Warts (1%)
  - Note: both pneumococcal and meningococcal vaccine antibody responses were unaffected in children using tacrolimus ointment
- While using tacrolimus, drinking alcohol may cause the skin or face to become flushed or red and feel hot

## TACROLIMUS BLACK BOXED WARNING[4,8-10]

- Systemic use of calcineurin inhibitors (IV, oral) for sustained immunosuppression in animal studies and transplant patients is associated with increased risk of infections, lymphomas, and skin malignancies.
- Black Boxed warning4: Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors (TCIs), including Tacrolimus Ointment. Therefore:
  - Continuous long-term use of TCIs, including tacrolimus Ointment, in any age group should be avoided
  - Application should be limited to areas of involvement
  - Tacrolimus is not indicated for children younger than 2 years of age and only 0.03% is indicated in children ages 2-15 years old
- This association has been extensively studied:
  - 2023 systematic review and meta-analysis in Lancet: there is “moderate-certainty evidence” to indicate topical calcineurin inhibitors do not increase the risk of cancer.9
  - 2021 systematic review and meta-analysis in JAMA Derm: There is a potential association between TCI use and risk of lymphoma but not other cancers, though given the low absolute risk, the increased risk attributable to TCI use for any individual patient is likely very small.10

## GENERAL PRECAUTIONS

- Avoid use on pre-malignant and malignant skin conditions and on skin infections
- Has not been studied in immunocompromised patients
- Avoid use in patients with skin barrier defects where there is potential for increased systemic absorption (Netherton’s syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease).
- Oral application of tacrolimus is not recommended as postmarketing cases of increased blood levels have been reported

## PREGNANCY AND BREASTFEEDING[4,5]

- Pregnancy Category C
- No data in pregnant women and only systemic tacrolimus data in rat and rabbit models
  - Tacrolimus is transferred across the placenta; the use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction
- Systemic tacrolimus is excreted in breast milk; there is no data on topical use

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