Pimecrolimus and Tacrolimus

Pimecrolimus and tacrolimus are used to treat atopic dermatitis, a type of eczema. The drugs are prescribed to children and adults. Pimecrolimus is applied as a cream directly to the affected skin until the condition is cleared. Tacrolimus is similarly applied as an ointment. Pimecrolimus and tacrolimus are calcineurin inhibitors, *i.e*., they inactivate calcineurin, thereby suppressing the immune response. They have been used since the year 2000 as alternatives to steroids for the treatment of atopic dermatitis. Tacrolimus also has long been used as a systemic drug by injection or ingestion for immunosuppression in organ transplant patients.

Pimecrolimus passed the animal data screen. Tacrolimus passed the human data screen. Each compound underwent a preliminary toxicological evaluation, and each is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified on each compound during the preliminary toxicological evaluations. Pimecrolimus and tacrolimus are presented together because of their similarity in structure and biologic activity. The CIC is being asked to advise OEHHA on whether either chemical should be brought to the committee for a full evaluation of the carcinogenicity evidence at a future meeting.

Epidemiolgical data

Pimecrolimus

- Topical application
    - Retrospective cohort study
        - *Possible risk of T-cell lymphoma*: Hui *et al.* (2009)
    - Case-control study
        - *No association between use and lymphoma*: Arellano *et al.* (2007)
    - Case reports
        - *Cutaneous tumors (6 cases) and lymphomas (4 cases)*: Reviewed by Wooltorton (2005)

Tacrolimus

- Injection or oral administration
    - Case-control study - 1000 liver transplant patients
        - *Increased risks of oropharyngeal (oral cavity, pharynx and larynx), respiratory and skin cancers*: Jain *et al.* (1998)
- Topical application
    - Retrospective cohort study
        - *Increased risk of T-cell lymphoma*: Hui *et al*. (2009)

- Case-control study
  - *No association between use and lymphoma*: Arellano *et al.* (2007)

Case reports

- *Lymphomas (9 cases) and skin tumors (squamous cell carcinoma, cutaneous sarcoma and malignant melanoma) (10 cases)*: Reviewed by Wooltorton (2005)
- *Skin squamous cell carcinoma at site of application*: Langeland and Engh (2005); von Felbert *et al.* (2010)

Animal carcinogenicity data

Pimecrolimus

- Studies in rats
  - Two-year dermal studies in male and female Wistar rats: FDA (2001), FDA Approved Label (2010)
    - *Increase in thyroid follicular cell adenoma in males (by pairwise comparison and trend)*
    - *No treatment-related thyroid tumors in females*
  - Two-year gavage studies in male and female Wistar rats (study #1): FDA (2001, pp. 6-8); FDA Approved Label (2010)
    - *Increase in benign thyomas in males*
    - *No treatment-related tumor findings in females*
  - Two-year gavage studies in male and female Wistar rats (study #2): FDA (2001, pp. 6-8); FDA Approved Label (2010)
    - *Increase in benign thyomas in males and females (by pairwise comparison)*
- Studies in mice
  - Gavage carcinogenicity studies in male and female mice: FDA Approved Label (2010)
    - *Increase in lymphomas in males and females (by pairwise comparison)*
  - Dermal carcinogenicity study in mice: FDA Approved Label (2010)
    - *No treatment-related tumor findings*
  - Dermal 13-week repeat dose study in mice: FDA Approved Label (2010)
    - *Increase in lymphomas and other lymphoproliferative lesions*
- Study in monkeys
  - Oral 39-week toxicity study in monkeys: FDA Approved Label (2010)

        - *Immunosuppressive-related lymphoproliferative disorder (IRLD) associated with lymphocryptovirus (simian analog of human Epstein Barr virus). IRLD is a precancerous condition that can progress to lymphoma in monkeys and humans.*

Tacrolimus

- Studies in rats
    - 104-week diet studies in male and female rats: FDA Approved Label (2006)
        - *No treatment-related tumor findings in males or females*
- Studies in mice
    - 80-week diet studies in male and female mice: FDA Approved Label (2006)
        - *No treatment related tumor findings in males or females*
    - 104-week dermal studies in male and female mice: FDA Approved Label (2006)
        - *Increase in lymphomas in males and females (by pairwise comparison)*
    - 20-week dermal initiation-promotion study in female mice (tacrolimus as co-promoter with 12-*O*-tetradecanoylphorbol-13-acetate; 7,12-dimethylbenz[a]anthracene as initiator): Niwa *et al*. (2003)
        - *Increase in skin papilloma, and papilloma and carcinoma (combined)*

Other relevant data

- Genotoxicity

  Pimecrolimus
    - Review: FDA Approved Label (2010)
        - *No evidence of genotoxicity in a battery of in vitro tests or in a mouse in vivo micronucleus assay*

  Tacrolimus
    - Review: FDA Approved Label (2006)
        - *No evidence of genotoxicity in bacteria, mammalian cells in culture, mouse in vivo clastogenicity assays, or unscheduled DNA synthesis assays in rodent hepatocytes*

- Mode of action considerations
    - Like the known human carcinogen cyclosporine, pimecrolimus and tacrolimus are immunosuppressive drugs that are calcineurin inhibitors. Cyclosporine causes lymphoma, skin and other cancers.

- Dermal tacrolimus in mice decreases CD4/CD8 helper cell ratio, a risk factor for malignancy: Niwa *et al.* (2003)
- Tacrolimus and other immunosuppressive drugs increase the incidence of chromosomal aberrations and tumors in mice exposed to UVB radiation: Dworkin *et al*. (2009)

References[1]

Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF (2007). Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* **127**:808-816.

Dworkin AM, Tober KL, Duncan FJ, Yu L, Van Buskirk AM, Obersyzyn TM, Toland AE (2009). Chromosomal aberrations in UVB-induced tumors of immunosuppressed mice. *Genes Chromo Cancer* **48**(6):490-501.

Food and Drug Administration (FDA, 2001) Center for Drug Evaluation and Research, Application Number: 21-302, Pharmacological Review (completed 11/8/01).

FDA Approved Label (2006) Protopic® Ointment (Tacrolimus), NDA 50-777/S-012 (Approved 1/19/2006).

FDA Approved Label (2010) Elidel® Cream 1% (Pimecrolimus), final printed labeling, NDA 21-302, revised July 2010.

Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, Millares M (2009). Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* **43**(12):1956-63.

Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, Zak M, Rakela J, Irish W, Fung JJ (1998). Comparative incidence of *de novo* nonlymphoid malignancies after liver transplantation under tacrolimus using Surveillance Epidemiologic End Result data. *Transplantation* **66**:1193-1200.

Langeland T, Engh V (2005). Topical use of tacrolimus and squamous cell carcinoma of the penis. *Br J Dermatol* **152**:183-185.

Niwa Y, Terashima T, Sumi H (2003). Topical application of the immunosuppressant tacrolimus accelerates carcinogenesis in mouse skin. *Br J Dermatol* **149**:960-967.

Von Felbert V, Hampl M, Talhari C, Engers R, Megahed M (2010). Squamous cell carcinoma arising from a localized vlval lesion of Hailey-Hailey disease after tacrolimus therapy, *Am J Obstet Gynecol* **203**(3):e5-7.

Wooltorton (2005) Eczema drugs tacrolimus (Protopic®) and pimecrolimus (Elidel®): cancer concerns. *CMAJ* **172**(9):1179-1180.

[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.