September 20, 2011

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Subject: Comments on Pimecrolimus/Tacrolimus as a priority chemical for review by the Carcinogen Identification Committee

Dear Ms. Oshita:

On behalf of the California Healthcare Institute (CHI), I’m writing regarding the upcoming Carcinogen Identification Committee (CIC) meeting on October 12th and 13th, at which CIC members will be reviewing Tacrolimus in order to provide advice to the Office of Environmental Health Hazard Assessment (OEHHA) on the prioritization of these chemicals as carcinogens under Proposition 65. The California Healthcare Institute is a statewide trade association representing more than 270 of our state’s premier biomedical and life science companies and academic research institutions.

According to the OEHHA notice from July 22, 2011, the CIC will be using several studies in their assessment of Pimecrolimus’ and Tacrolimus’ carcinogenicity, in particular, the epidemiological studies by Hui et al and Jain et al, which are being used to allege human carcinogenicity when used topically or when injected or administered orally, respectively. However, upon our review of these studies and other supporting data it is our belief that no prioritization should be given to Tacrolimus or Pimecrolimus by the CIC.

The first study, Hui et al, was a retrospective cohort observational study using data from 953,064 subjects with diagnoses of atopic dermatitis between 2001 and December 2004. The study’s objective was to determine whether or not patients exposed to topical Tacrolimus or Pimecrolimus for the treatment of various dermatological conditions were at greater risk of developing cancer than other patients who were not exposed to Tacrolimus. Of the 953,064 patients with atopic dermatitis, 38,682 were exposed to Tacrolimus alone and only 9 individuals from that cohort developed T-cell lymphoma. While this difference is of statistical relevance, it still does not fully correlate that the application of topical Tacrolimus causes T-cell lymphoma,
nor did the study show an overall increased risk of developing cancer. In fact, Dr. Hui addresses two important limitations in the study:

“The median follow-up time from Tacrolimus and Pimecrolimus exposure to the end of the study was only 2.4 and 1.9 years, respectively. This may not be a long enough follow-up time to determine the full effects of these topical agents. Secondly, there may be protopathic bias, which occurs if the first symptoms of the endpoints are the reasons for using the treatment. In our case, a topical calcineurin inhibitor was being used to treat what appeared to be a minor skin condition, but which was an early manifestation of cutaneous T-cell lymphoma (CTCL).”

These limitations are significant enough that we believe that the study should not be used as a basis for determining the carcinogenicity of either of these drugs. If the timeframe of study and improper initial diagnosis are believed to be problems by the study’s author we would question the need to include it to corroborate the prioritization of Tacrolimus as a carcinogen. Furthermore, Dr. Hui and her colleagues conclude their study by stating that “further study with longer follow-up time is needed to support our findings.”

The second study, Jain et al, looked at 1,000 patients who received liver transplants from a single center and received oral or injected Tacrolimus treatment for immunosuppressive purposes. While the study was able to conclusively determine that recipients of liver transplants who used Tacrolimus in order to prevent organ rejection did see an in increased rate of oropharyngeal cancer up to 7.6 times greater when compared to the general population, it wasn’t entirely conclusive on the causal link between de novo oropharyngeal malignancy development and the use of Tacrolimus. One of the primary risk factors for oropharyngeal cancer is alcoholic liver disease (ALD). As Jain et al note in their study, “rates of oropharyngeal cancer and lung cancers (were) 25.5 and 3.7 times greater in the ALD group compared with the general population.”

Lending further credence to the role that alcoholism plays in cancer development in transplant patients they state that “70% of patients who developed oropharyngeal, lung and gastrointestinal cancers in the study had an alcoholic history before liver transplant.”

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Furthermore, it is well documented, in this study and others, that transplant recipients have a high likelihood to develop Post-Transplant Lymphoproliferative Disorder (PTLD), a condition wherein B-cells proliferate, far in excess of what is normal or healthy, causing some to undergo mutation, and in doing so, becoming malignant. Calcineurin inhibitors, like Tacrolimus, when used as immunosuppressants can exacerbate PTLD and PTLD-related malignancies by intentionally inhibiting T-cell function, a necessary part of preventing organ rejection, but can also prevent T-cells from actively monitoring for other malignant or tumorous cells that they might otherwise find. Therefore, while one might infer from the study that de novo tumor development could increase as an indirect consequence of purposefully suppressing the immune system using Tacrolimus in order to prevent organ rejection post-transplant or as a consequence of behavioral factors such as alcoholism. However, we do not believe that this study is able to state emphatically that Tacrolimus, in and of itself, does indeed cause cancer in patients who are administered the drug orally or intravenously.

In closing, we believe that the current literature regarding Tacrolimus exposure presents an inadequate case for making the drug a candidate for prioritization. Neither epidemiological study was able to prove categorically that Tacrolimus when taken orally, topically or injected causes the development of cancer. Additionally, if one of the criteria for prioritization of a chemical for Proposition 65 is public exposure, then we do not believe that Tacrolimus meets that test, either. Furthermore, Tacrolimus, as a prescription drug, went through a rigorous FDA review process before being permitted for medical use. With only a few FDA approved applications, exposure would only occur in limited instances and only after an informed consent process with one’s physician or medical practitioner where the therapeutic benefits and health risks are thoroughly considered.

Because of the aforementioned reasons we do not feel that Tacrolimus should be deemed a priority chemical by the CIC. Thank you for the opportunity to submit these comments.

Sincerely,

Consuelo Hernandez
Vice President of State Government Affairs
California Healthcare Institute