DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-723

3M Pharmaceuticals
Attention: Mark A. Morken, RPh
Senior Regulatory Associate
3M Center, Building 270-3A-08
St. Paul, Minnesota 55144-1000

Dear Mr. Morken:

Reference is made to your Proposed Pediatric Study Request submitted on November 1, 2001, for Aldara (imiquimod) Cream, 5%.

To obtain needed pediatric information on imiquimod the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Background:

Molluscum contagiosum is a contagious disease caused by a pox virus and largely affects children. It is characterized by skin lesions that are waxy in appearance with central umbilication that usually number from 2-20. Pediatric patients with primary or secondary immunosuppression usually have much greater numbers of lesions than those with normal immune systems.

Mechanical removal of the central core usually results in resolution. Alternatively, topical application of catharidin, peeling agents such as salicylic and lactic acid preparations, or liquid nitrogen may be successful. Although lesions can spontaneously regress, removal is advisable when possible to avoid autoinoculation and spread to other individuals. Immunosuppressed patients are more difficult to treat and are less likely to have lesions that spontaneously regress.

Aldara™ (imiquimod) Cream, 5% is approved for the treatment of external anogenital warts in adults. This product is an immune response modifier, which is being used off-label in the United States to treat molluscum contagiosum in children. The safety and efficacy of this product for the treatment of Molluscum contagiosum has not been established in well controlled clinical

Type of studies to be performed:

Study 1: Clinical safety and efficacy studies in pediatric patients with normal immune function with molluscum contagiosum.

Study 2: Clinical safety and efficacy studies in immunocompromised pediatric patients with molluscum contagiosum.

Study 3: Pharmacokinetic study in patients with molluscum contagiosum. The patients enrolled should have multiple lesions (greater than 5) to be treated with at least 25% of the patients having more than 10 lesions.

Indication to be studied: Treatment of molluscum contagiosum in pediatric patients.

Study Design:
Study 1: Randomized, multi-center, placebo-controlled, double blind trials in immunocompetant pediatric patients with molluscum contagiosum.

Study 2: Randomized, multi-center, placebo-controlled, double blind trials in immunocompromised pediatric patients with molluscum contagiosum.

Study 3: A multiple dose pharmacokinetic study using the product in a manner consistent with clinical efficacy and safety trials, with pharmacokinetic sampling done at the end of Week 1 and Week 4.

Clinical endpoints:

Study 1: Complete clinical resolution of the molluscum lesions.

Study 2: Complete or partial resolution of the molluscum lesions.

Safety endpoints:

Special attention should be given to ocular function in those patients who are enrolled with periocular lesions. Local irritation, ulceration, post-treatment scarring and pigmentation changes. All other safety data obtained in this study.

Study evaluation:

Studies 1 and 2: Weekly for a total of 16 weeks. All subjects who clear, regardless of treatment assignment, will be followed for an additional 12 weeks post-treatment to evaluate recurrence, post-treatment adverse events, and cosmetic condition of the

treatment area. Non-cleared subjects at 16-week end-of-treatment visit will be offered appropriate standard of care.

Study 3: The pharmacokinetic parameters for imiquimod and its metabolite should be determined after muli-dose and at steady state (e.g. AUC, Cmax, Tmax and CL/F)

Number of patients to be studied or power of study to be achieved:
Studies 1 and 2: In order to have an adequate safety database, at least 300 pediatric patients exposed to imiquimod cream 5% must complete these studies. This number may be different from the number of patients needed to demonstrate efficacy.

To assess the safety of using imiquimod in periocular lesions, at least 25 patients from these two studies should have periocular lesions that were treated with imiquimod.

Study 1: For efficacy, these studies should be powered to detect a statistically significant difference between treatment groups (imiquimod and placebo). The studies should be powered to show that imiquimod is superior to placebo for the complete clinical cure (total lesion clearance) of molluscum contagiosum.

At least 50% of the patients should have at least 5 lesions, with no upper limit on the number of lesions. At least 20% of patients enrolled should have periocular molluscum contagiosum.

Study 2: For efficacy, these studies should be powered to detect a statistically significant difference between treatment groups (imiquimod and placebo). The studies should be powered to show that imiquimod is superior to placebo for the complete clinical cure (total lesion clearance), or improvement of molluscum contagiosum.

Study 3: At least 15 immunocompetent patients and 15 immunocompramised patients to assess systemic exposure

Drug Information:

Formulation: Imiquimod cream, 5%

Route of administration: Topical, applied to the lesion only

Regimen: Applied only to lesion 3 times weekly until resolution of the lesion.

Duration: Up to 16 weeks of treatment with adequate follow-up to assess recurrence, post-treatment adverse events, and cosmetic condition of the treatment area.

Drug specific safety concerns:

Local irritation to include ulceration and edema. Post-treatment scarring and pigmentation changes.

Age group on which studies should be performed:

Studies 1 and 2: Pediatric patients ages 2-12 years, with approximately even distribution throughout the age groups, and at least 50% of the patients below 6 years.

Study 3: Pediatric patients 2-12 years old with equal distribution across the entire age range.

Statistical information:

Studies 1 and 2: A superiority claim may be made based on the results of two well-controlled studies. The primary efficacy variable (clinical cure) will be analyzed using a Cochran Mantel Haenszel (CMH) test, stratified by center. Subgroup analysis should be performed on subgroups of patients determined by lesion count.

Adverse event and local irritation data should be summarized with standard descriptive statistics.

Study 3: Analysis of the pharmacokinetic parameters (e.g. AUC, Cmax, Tmax and CL/F) should include descriptive statistics for each parameter. The data should be analyzed in both pooled manner and in a stratified manner, based on number of lesions (≤ 5, >5)

Labeling that may result from the studies:

Information collected from this study should permit the determination of appropriate labeling for use of topical imiquimod cream, 5%, for the treatment of molluscum contagiosum in pediatric patients.

Format of reports to be submitted:

Full and final study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. We recommend that you follow the July, 1996 ICH (E3) guideline for structure and content of a clinical study report.

Timeframe for submitting reports of studies:

Reports of the above studies must be submitted to the Agency on or before January 29, 2004. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED**

FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.
We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please call Mildred Wright, Project Manager, at (301) 827-2020.

Sincerely yours,

Jonca Bull, M.D.
Acting Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Jane Walling

12/28/01 02:17:32 PM