DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #5

NDA 20-723

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

Dear Ms. Hupperts:

Please refer to your correspondence dated January 13, 2006, requesting changes to FDA's May 10, 2004 amended Written Request for pediatric studies for imiquimod cream, 5%.

We have reviewed your proposed changes and amended the Written Request with an amended Written Request issued on May 3, 2006. Due to a typographical error, the symbol #, instead of ≤ was placed in the parenthesis under Study 3, Statistical Information.

Study 3 under Statistical Information should read as follows:
Study 3: Analysis of the pharmacokinetic parameters (e.g. AUC, Cmax and Tmax) should include descriptive statistics for each parameter. The data should be analyzed in both a pooled manner and in a stratified manner, based on the percent body surface area involved and by age (less than or equal to five, greater than five).

For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Requests dated December 28, 2001, May 9, 2003, December 18, 2003, May 10, 2004, and May 3, 2006.

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 trials submitted to the Agency.

Type of studies to be performed:
Studies 1 & 2: Clinical safety and efficacy studies in pediatric patients with molluscum contagiosum.
Study 3: Pharmacokinetic study in patients with molluscum contagiosum. The patients enrolled should require application of Aldara Cream to greater than 10% body surface area to cover all lesions.

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

Study Design:
Studies 1 & 2: Randomized, multi-center, placebo-controlled, double blind trials in 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 after the first dose and at the end of Week 4.

Clinical endpoints:
Study 1 & 2: Complete clinical resolution of the molluscum lesions at week 18.

Safety endpoints:
Special attention should be given to ocular function in those patients who are enrolled and periocular lesions should be reported, as well as local irritation, ulceration, posttreatment scarring and pigmentation changes. All other safety data obtained in this study must also be reported.

Study evaluation:
Studies 1 and 2: Study evaluations at weeks 2, 4, 8, 12, 16 and 18. All subjects who clear, regardless of treatment assignment, will be followed for an additional 12 weeks posttreatment to evaluate recurrence, post-treatment adverse events, and cosmetic condition of the treatment area. Non-cleared subjects at the18-week efficacy assessment visit will be offered appropriate standard of care.
Study 3: The pharmacokinetic parameters for imiquimod and two metabolites should be determined after single dose and at steady state (e.g. AUC, Cmax and Tmax).

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 enrolled in these two studies should have periocular lesions that were treated with imiquimod. Periocular lesions are those lesions that occur within the area of skin around each eye bordered by the eyebrow, bridge of the nose, temple and cheekbone and at least 0.5 cm away from the edge of the eyelid.
Studies 1 & 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) 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 25 of the patients enrolled should have periocular molluscum contagiosum.
Study 3: At least 15 evaluable subjects should be enrolled to assess systemic exposure.

Drug Information:
Formulation: Aldara (imiquimod) Cream), 5%.
Route of administration: Topical, applied to affected areas.
Regimen: Applied to affected area 3 times weekly until resolution of the lesions.
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 at least 50% of the patients under 6 years and at least 20% of the patients under 4 years.
Study 3: Pediatric patients 2-12 years old should be about equally distributed 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 and Tmax) should include descriptive statistics for each parameter. The data should be analyzed in both a pooled manner and in a stratified manner, based on the percent body surface area involved and by age (less than or equal to five, greater than five).

Labeling that may result from the studies:
Information collected from this study should permit the determination of appropriate labeling for use of topical Aldara (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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of studies:
Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before December 29, 2006. Please keep in mind 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.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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.

Submit reports of the studies as a supplement to **NDA 20-723** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Felecia Curtis, Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Julie G. Beitz, M.D.
Acting Director
Office of Drug Evaluation III
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/

Julie Beitz

5/5/2006 05:38:01 PM