CLINICAL EXECUTIVE SUMMARY

Application Type	NDA
Submission Number	20723
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Letter Date	September 21, 2006
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Reviewer Name	Elektra J. Papadopoulos
Established Name	Imiquimod
Trade Name	Aldara
Applicant	3M
Priority Designation	P
Formulation	Imiquimod 5% cream
Dosing Regimen	Three times weekly
Indication	Molluscum Contagiosum
Intended Population	Children ages 2-12

I. Executive Summary

1.1 Recommendation on Regulatory Action

Aldara (imiquimod cream, 5%) is approved for use in children 12 years and older for the treatment of external genital/perianal warts with 3 times per week application for up to 16 weeks. Children below the age of 12 are treated off-label with Aldara for various skin disorders, including molluscum contagiosum (MC). To obtain safety and efficacy data for the treatment of MC in children, the FDA has issued a Written Request (Section 505A of the Federal Food, Drug, and Cosmetic Act) for evaluation of imiquimod for the treatment of MC in children 2-12 years of age. Three studies were requested, two independent, double-blind, vehicle-controlled safety and efficacy studies and 1 pharmacokinetic (PK) study. The studies were conducted according to the terms of the Written Request and Pediatric Exclusivity was granted by the Agency on December 13, 2006.

Efficacy was not demonstrated with 3 times per week topical application for up to 16 weeks in either of two independent phase 3 studies for the indication of MC in pediatric subjects 2-12 years of age. This reviewer recommends revision to package insert to include the findings from these two phase 3 clinical studies as well as the results of the PK study. The sponsor is not pursuing efficacy claims regarding MC, and this reviewer recommends revision to package insert to reflect that the treatment of MC is a limitation of use based on the negative results of these studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is needed other than revision of the package insert.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are indicated on the basis of this labeling supplement.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program included a phase 2 study, Study 1490-IMIQ, and two phase 3 studies, 1494-IMIQ and 1495-IMIQ, all in pediatric patients ages 2-12 years with MC. The two phase 3 study

protocols were very similar, and for practical purposes related to this review are considered identical. Both phase 3 studies included three times weekly dosing for up to 16 weeks. The phase 2 study included daily dosing (7 days per week) for up to 8 weeks.

1.3.2 Efficacy

This labeling supplement contains the reports of two phase 3, multicenter, randomized, vehicle-controlled clinical studies in pediatric subjects 2-12 years of age. Complete clearance of all MC lesions at Week 18 was the primary clinical endpoint in both phase 3 studies. The subset of subjects with periocular MC also failed to show any trend of treatment benefit. In 1494-IMIQ, the complete clearance rate was 24% (52/217) in the Aldara Cream group compared with 26% (28/106) in the vehicle group. In 1495-IMIQ, the clearance rates were 24% (60/253) in the Aldara Cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy.

1.3.3 Safety

In the combined phase 3 study data, the most frequently reported possibly or probably related adverse event (AE) was application site reaction; 31% (144/470) of Aldara-treated subjects and 20% (47/232) of vehicle-treated subjects reported at least one application site reaction. Nine subjects discontinued a study due to an AE; 6 Aldara-treated subjects and 3 vehicle-treated subjects. The most common adverse events were application site reactions.

Local skin reactions (LSR) were recorded separately from adverse events. The most frequently recorded investigator-assessed LSR was erythema, where 93% (426/460) of imiquimod and 87% (195/223) of vehicle-treated subjects experienced erythema (any severity). A total of 73% (336/460) of imiquimod and 55% (122/223) of vehicle subjects had moderate or severe erythema at least once after treatment initiation. This is in keeping with the known local reaction profile of Aldara from use in other indications.

In the subgroup of subjects with periocular MC, erythema was the most frequently reported LSR. Fifty percent of subjects reported mild/moderate erythema as the most intense LSR in the periocular region during the study (no severe erythema was reported). Flaking/scaling/dryness was the second most frequently reported LSR, with 31% of subjects reporting. One severe LSR was reported in the periocular region in one patient (severe flaking/scaling/dryness). The remainder of LSR in the periocular region were either mild or moderate in maximum intensity.

In the phase 3 studies, the investigator could prescribe a rest period if the subject experienced signs or symptoms at the treatment site that restricted their daily activities or made continued application of the study cream difficult. In Study 1494, the 9% (19/217) of Aldara-treated subjects took a rest period compared with 4% (4/106) vehicle-treated subjects. In Study 1495, 6% (15/253) of Aldara-treated subjects took a rest period compared to 2% (2/126) of vehicle-treated subjects.

In the phase 3 studies, a subgroup of patients had hematologic assessments at baseline and following the end of treatment. A higher incidence rate of shift from normal WBC at baseline to below normal after the end of treatment in white blood cell (WBC) parameters in the imiquimod

group was observed compared with vehicle control. In the Aldara group 13% (10/79) had a decrease from normal to below normal WBC count compared to 7% in vehicle (3/42). For absolute neutrophil counts, 12% of Aldara patients (9/78) and 5% of vehicle-treated patients (2/41) had decrease from normal to below normal. In the PK study where the drug was studied under maximum use conditions (minimum body surface area treated was 10%), 8 of 20 Aldara-treated subjects experienced shifts from normal to below normal absolute WBC count and 5 of 20 experienced shifts from normal to below normal absolute neutrophil counts. In this study, the median WBC count decreased by $1.4*10^9$/L and the median absolute neutrophil count decreased by $1.42*10^9$/L. The time to resolution of the low WBC parameters was not studied. It is possible that these findings may be due to systemic effects of imiquimod.

Other safety findings from the clinical trials included a higher rate of lymphadenopathy in the imiquimod group compared with control. While the difference between treatment groups overall was modest, 3% (14/470) in the Aldara group compared with 2% (5/232) in the vehicle group, the difference between treatment groups was highest in the <4 years of age subgroup, where the incidence rate was 7% (8/124) in the Aldara group compared with 0% (0/57) in the vehicle group.

Safety findings from spontaneous reports have included several unlabeled adverse reactions. A search of the AERS database revealed nine cases of erythema multiforme occurring in adult patients and four of the nine cases involved hospitalization. Another safety finding included a case of Henoch-Shonlein purpura in a 3 year-old boy treated for MC with Aldara. Finally, a case of treatment-emergent idiopathic thrombocytopenic purpura was reported in a child who had been receiving Aldara for MC. It is recommended that these adverse reactions be described in labeling.

1.3.4 Dosing Regimen and Administration

The dosing regimen studied in the clinical trials was 3 doses per week topically to skin affected by MC for up to 16 weeks (48 doses), stopping prior to 16 weeks of treatment if the investigator determined the subject was completely clear of MC lesions. Subjects weighing <25 kg were to apply up to 2 packets per dose application while subjects weighing ≥25 kg could apply up to 3 packets per dose application. Each packet contains 250 mg of cream, or 12.5 mg imiquimod.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were carried out under a pediatric Written Request and the Agency has granted the sponsor's request for pediatric exclusivity.

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/s/

Stanka Kukich

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