CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201153Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 17th, 2011
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA/Supplement #	201153/S-001
Applicant Name	Graceway
Date of Submission	February 12th, 2010
PDUFA Goal Date	December 8th, 2010
Proprietary Name / Established (USAN) Name	Zyclara/imiquimod
Dosage Forms / Strength	Cream/3.75%
Proposed Indication(s)	1. Treatment of external genital warts (condyloma acuminata)
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Milena Lolic, M.D.
Statistical Review	Kathy Fritsch, PhD, Mohamed Alosh, PhD (TL)
Pharmacology Toxicology Review	Jianyong Wang, PhD; Barbara Hill, PhD (TL)
Clinical Pharmacology Review	Dennis Bashaw, PhD (Div Dir)
CMC	Shulin Ding, PhD.
DDMAC	Christine Corser, PharmD.
CDTL Review	Jill Lindstrom, M.D.
OSE/DMEPA	Cathy Miller, MPH, BSN
OSE/DRISK	Latonia Ford, RN.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

The applicant has submitted an efficacy supplement proposing the approval of currently marketed imiquimod cream 3.75% to be used daily for up to 8 weeks for the treatment of genital warts. The sponsor markets a higher strength cream, imiquimod 5%, for the treatment of genital warts when used three times weekly for up to 16 weeks.

2. Background

No chemistry, pharmacology, toxicology, or biopharmaceutics issues are raised with this application. The application proposes a lower strength cream to be used more frequently than the currently marketed product for the same indication – treatment of genital warts.

External genital warts (condyloma) occur on the cutaneous genital surfaces of both men and women. The optimal objective of dermatologic treatment is to eradicate these lesions, and there are several choices available to physicians, including both drug and non-drug therapies such as podophyllin, cryotherapy with liquid nitrogen, laser therapy, electrosurgery, excision, and interferons/imiquimod.

The degree to which a therapy eradicates the visible wart has not been demonstrated to be critical to the health or safety of a patient. The Centers for Disease Control (CDC) recently noted [1] that "no definitive evidence suggests that any of the available treatments are superior to any other, and no single treatment is ideal for all patients or all warts. ….Because of uncertainty regarding the effect of treatment on future transmission of HPV and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution". The cross discipline team leader has presented a very thoughtful discussion of pertinent issues and recommended a "complete response" based upon lack of evidence to support the new dose and dose interval, with a recommendation for conducting an active and vehicle-controlled trial of the safety and efficacy of the proposed 3.75% strength and the currently marketed 5% strength of imiquimod cream in the treatment of external genital warts. While I am in complete agreement that this information would be useful as additional clinical information, I believe that it is not necessary in order to establish the safety or efficacy of the proposed treatment regimen.

3. CMC/Device

[1] The Morbidity and Mortality Report of 17 December 2010: Sexually Transmitted Disease Guidelines,

I concur with the conclusions reached by the chemistry reviewer Dr. Shulin Ding regarding the acceptability of the manufacturing of the drug product and drug substance. The application has provided sufficient information to assure the identity, strength, purity and quality of the drug product. All facilities are in compliance with cGMP and labels/labeling have adequate information required. There are no outstanding issues."

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The conduct and design of the clinical pharmacology studies was consistent with discussions and advice given to the sponsor.

The bioavailability of imiquimod cream applied topically appears to be relatively low. Although direct comparisons are not available, the daily application of one packet of imiquimod 3.75% cream resulted in similar detectable levels (Cmax 0.488 ng/ml) as imiquimod 5% cream used three times weekly (Cmax 0.437 ng/ml).

As summarized by Dr Bashaw, study GW01-0804 was designed to characterize the pharmacokinetic profile of daily applications of 3.75% imiquimod cream under anticipated maximal use conditions in subjects with external genital warts. Serum concentrations of imiquimod and of the two combined major metabolites (S-26704/ S-27700) were measured by the analytical method with a lower limit of quantitation (LLOQ) of 0.05 ng/mL. The study was conducted under maximal use conditions (dose, duration, disease severity, and application areas) in a population with at least 8 warts in the genital/perianal area or a total wart area of ≥100mm2, applying once daily applications of up to 1 packet of 3.75% imiquimod cream for 3 continuous weeks (21 days). The three week period was selected to confirm that steady-state conditions would exist, based upon a demonstrated half-life of 3.4 to 33.4 hrs for imiquimod 5% cream. Additional details can be obtained in the Biopharm review. Mean serum concentrations ranged from 0.16 to 0.37 ng/mL on Day 21, with median Tmax of 12 hours on Day 1 and 21, mean effective half-life for accumulation of 31.3 hours, and observed mean elimination half-life of 24 hrs on Day 21. Based upon the observed data and discussions by the Biopharm reviewer, it appears that steady state could occur somewhere between 7 and 14 days. I concur with the reviewer's discussion of the principles of a maximal use trial and agree that this study is acceptable, including a good assay that was able to detect plasma samples in all subjects above the LLOQ.

6. Clinical/Statistical-Efficacy

Zyclara (imiquimod) cream 3.75% applied once daily for up to 8 weeks was superior to vehicle in the treatment of external genital warts in two studies ($p \leq 0.001$, statistically significant after adjusting for multiplicity due to two dose groups). The studies also evaluated imiquimod cream 2.5% which was only superior to vehicle in one of the two studies. The studies enrolled subjects at least 12 years of age with 2-30 genital/perianal warts with a total wart area of at least 10 mm2. The primary efficacy endpoint was complete clearance of all warts (baseline and new) on or before Week 16 as determined by the investigator. Subjects stopped treatment when/if complete clearance was achieved in less than 8 weeks, and had the end-of-study visit 8 weeks following the end of treatment. Otherwise, subjects applied imiquimod cream daily for 8 weeks and then discontinued treatment, and had an end-of study evaluation at study week 16. Clearance rates were consistently higher in female subjects than male subjects.

Overall, approximately 28% of imiquimod 3.75% subjects vs. 9% of vehicle subjects achieved complete clearance.

Complete Clearance Rates at End of Study (ITT)

Study	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	53/195 (27%) 0.001*	34/178 (19%) 0.065	10/97 (10%)
0805	60/204 (29%) <0.001*	50/202 (25%) 0.001*	9/105 (9%)

The CDTL review expresses concerns regarding the lack of comparative efficacy data provided in this application, specifically, the study lacks a within-trial comparison with the currently approved 5% imiquimod cream for the treatment of EGW. While I fully concur that such information would extend and optimize the available information regarding the performance of imiquimod cream in this indication, I do not concur that this information is necessary for approval of the proposed dosage and dosing regimen. Neither treatment includes a claim to eradicate genital warts or to prevent viral transmission, and the labeling for each regimen provides clear information regarding outcomes. While cross study comparisons are hazardous, the simple labeling for each product is informative, demonstrating that a significant number of patients treated with each regimen did not achieve complete clearance. The labeling for each product has adequate information to inform the prescriber/patients choice in regards to dosage, dosing regimen, and outcomes. The clinical reviewer has recommended approval.

7. Safety

The safety of imiquimod 3.75% topical cream has been evaluated in the clinical review by Dr. Lolic and her conclusions will be summarized here. The database for safety evaluation consisted of 400 subjects between the ages of 17-81 randomized to treatment with 3.75% imiquimod cream. An additional 379 subjects were randomized to treatment with imiquimod cream 2.5%. Safety evaluations consisted of analysis of reported adverse events, local cutaneous reactions, vitals signs, and laboratory testing. The most common adverse events were application site pain and irritation, which is consistent with the anticipated local effects of imiquimod cream. Local erythema was reported in 70% of subjects treated with active, with erosion/ulcerations reported in 11%. Approximately one third of patients utilized rest periods due to local adverse reactions.

The applicant did not include a comparator arm utilizing treatment with their currently marketed imiquimod 5% product; therefore, no reliable information is available to inform any comparisons between the 5% and 3.75% product regimens. In my opinion, product labeling is adequate to inform physicians regarding the performance of this new dosage and dosing regimen.

8. Advisory Committee Meeting

The application was not presented to an Advisory Committee. Imiquimod is not a new molecular entity and review of the application did not present or identify any novel issues requiring discussion.

9. Pediatrics

The applicant requested a partial waiver for the pediatric age group less than 12 years of age because the necessary studies would be highly impractical based on the small number and geographical dispersion of patients with EGW in that age group. The applicant completed studies with their product in patients 12 years of age and older, including adults.
The efficacy of imiquimod 3.75% cream in pediatric patients aged 12 years and older could be extrapolated from adult data because, although disease prevalence varies with age, the pathophysiology is understood to be the same in adolescents and adults. Additionally, there are not known age-related factors that would make the disease either more or less responsive to treatment in adolescents than adults.

The pivotal trials and the PK study allowed for inclusion of subjects 12 years and older; however, enrollment was limited to 3 subjects in the pivotal trials and one subject in the PK study. Supportive pediatric safety data includes the AERS database for imiquimod 5% cream (indicated for the treatment of external genital warts in subjects 12 years of age and older), and safety data from studies conducted in accordance with a Pediatric Written Request in pediatric subjects aged 2 to 12 years of age with molluscum contagiosum. Safety data generated in adult subjects is also supportive. Consultation was obtained from the Pediatric and Maternal Health Staff, who found the direct and supportive data sufficient to allow for a finding of safety in subjects 12 years of age and older with external genital warts.

The application was presented to the Pediatric Review Committee (PeRC) on 29 September 2010. The PeRC concurred with the Division's position that the applicant's request for a waiver should be granted for patients younger than 12 years of age. The PeRC agreed that efficacy data was not needed in pediatric adolescent subjects, but could be extrapolated from adequate adult data, and that the application contained adequate data for a determination of safety.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

Labeling discussions have been concluded with the sponsor and the approved labeling will provide information to inform prescribers and patients regarding the safety and efficacy of imiquimod cream 3.75% for the treatment of external genital warts.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment – The benefits of treatment with 3.75% imiquimod cream outweigh the risks of treatment. The selection of the most appropriate treatment modality and regimen can be determined by the prescriber.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments - None

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/s/

SUSAN J WALKER
03/23/2011