CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22483Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

To: NDA 22483
From: Jianyong Wang, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date:	01/29/2010
Serial No:	SDN 22
Submission type:	Resubmission/Class 1
Drug:	Zyclara (Imiquimod) cream, 3.75%
Drug class:	Immune modulator (cytokine inducer)
Indication:	Actinic keratosis (AK)
Route:	Topical
Sponsor:	Graceway Pharmaceuticals, Bristol, TN

Review date: 02/04/2010

Introduction:

NDA 22483 was submitted on 12/19/2008, and a complete response letter was sent to the sponsor on 10/16/2009. There were no nonclinical requests/recommendations in the complete response letter. This submission is a complete response from the sponsor to the complete response letter (10/16/2009) and it is considered a Class 1 resubmission. No nonclinical information was included in this submission.

Review of nonclinical toxicology study reports: None.

Discussion and conclusions:

No new nonclinical information was included in this submission. Please refer to the nonclinical review for NDA 22483 (08/03/2009) for pharmacology/toxicology information. An updated version of proposed drug labeling was included in this submission; however, there were no changes in the nonclinical portions of the labeling, compared with the previous version that was submitted to the original NDA. The recommended wording for nonclinical portions remains the same, which is provided in the next section.

Based on the nonclinical data available for oral imiquimod and imiquimod cream, NDA 22-483 [Zyclara (imiquimod) Cream, 3.75%] for the treatment of actinic keratosis is approvable from a pharmacology/toxicology perspective, (b) (4)

(b) (4)

(b) (4)

3 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	ORIG-1	GRACEWAY PHARMACEUTICALS LLC	IMIQUIMOD 3.75% CREAM

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

/s/

JIANYONG WANG
02/22/2010

BARBARA A HILL
02/22/2010
I concur

Division of Dermatology and Dental Drug Products
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date:	1-26-2009
Reviewer:	Jianyong Wang
NDA Number:	22-483
Drug Name:	imiquimod cream, 3.75%
CAS Number:	99011-02-6
Drug Class:	Immune modulator (cytokine inducer)
Indication:	Actinic keratosis
Route of Administration:	Topical
Date CDER Received:	12-19-2008
User Fee Date:	10-18-2009
Date of Draft Review:	7-31-2009
Sponsor:	Graceway pharmaceuticals, Bristol, Tennessee

Fileability:
On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

This is an electronic CTD NDA submission.

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? YES

Summaries of the required studies are submitted to this NDA; the study reports are referred to previous NDA/INDs.

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? YES

The nonclinical toxicology studies conducted with Aldara (imiquimod) cream, 5% are adequate to characterize the toxicity profile for the 3.75% imiquimod cream formulation.

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? YES

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? YES

Summaries of the required studies are submitted to this NDA; the study reports are referred to previous NDA/INDs.

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? YES

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? YES

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? YES

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? YES

(12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. YES

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: YES

It is recommended that the following information be relayed to the sponsor:
In the submission (2.3.P.5.5.1), you stated that a drug related impurity, most likely [redacted] was identified during the stability studies. The quantity of this 3 page

impurity in the drug product that was used in clinical studies, and if possible, in the drug product that was used in toxicology studies as well, needs to be provided for safety evaluation.

(14) Issues that should not be conveyed to the Sponsor: N/A

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

/s/

Jianyong Wang
2/17/2009 11:18:37 AM
PHARMACOLOGIST

Barbara Hill
2/17/2009 11:21:54 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-483**
SERIAL NUMBER:	**001**
DATE RECEIVED BY CENTER:	**12/19/2008**
PRODUCT:	**Zyclara (Imiquimod) cream 3.75%**
INTENDED CLINICAL POPULATION:	**Actinic Keratosis on the face and/or scalp**
SPONSOR:	**Graceway Pharmaceuticals, LLC**
DOCUMENTS REVIEWED:	**Electronic CTD NDA submission**
REVIEW DIVISION:	**Division of Dermatology and Dental Products (HFD-540)**
PHARM/TOX REVIEWER:	**Jianyong Wang, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barbara Hill, Ph.D.**
DIVISION DIRECTOR:	**Susan Walker, M.D.**
PROJECT MANAGER:	**Kelisha Turner**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The NDA for drug product Zyclara (Imiquimod) 3.75% cream is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – None

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested Labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings - Long term systemic exposure to imiquimod leads to immune system exhaustion, which leads to toxic effects that mimic traditional immune suppression.

B. Pharmacologic activity - Imiquimod is an immune modulator.

C. Nonclinical safety issues relevant to clinical use - Possible concern is raised for the formation of skin papillomas at the treatment site with the use of vehicle cream in the mouse dermal carcinogenicity study and the enhancement of UVR-induced skin tumor development noted after topical administration of the vehicle cream in the mouse photoco-carcinogenicity study.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

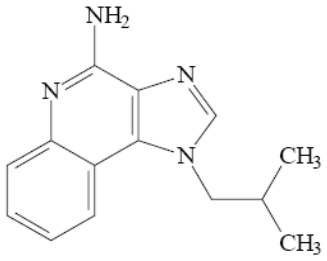
NDA number: 22-483
Review number: 1
Sequence number/date/type of submission: 1 / 12-19-08 / Original NDA submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Graceway Pharmaceuticals, LLC
Bristol, TN, 37620

Manufacturer for drug substance:

Reviewer name: Jianyong Wang
Division name: Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 8-1-09

Drug:

Trade name: Zyclara 3.75% cream
Generic name: Imiquimod 3.75% cream
Code name: R-837, S-26308
Chemical name: 1-(2-methypropyl)-1 *H*-imidazo[4,5-c]quinoline-4-amine
CAS registry number: 99011-02-6
Molecular formula/molecular weight: $C_{14}H_{16}N_4$ / 240.3
Structure:



Relevant INDs/NDAs/DMFs:

1) (b) (4)
2) (b) (4))
3) (b) (4))
4) IND 30,432 (imiquimod 5% cream; external genital/perianal warts; HFD-540)
5) IND 49,464 (imiquimod 5% cream; basal cell carcinoma; HFD-540)
6) IND 49,480 (imiquimod 5% cream; actinic keratosis; HFD-540)
7) (b) (4))
8) (b) (4))
9) (b) (4)

10) (b) (4)
11) (b) (4)
12) (b) (4)
13) NDA 20-723 (Aldara {imiquimod} 5% cream; external genital/perianal warts; HFD-540; Approved 2-27-97)

Drug class: Immune modulator (cytokine inducer)

Intended clinical population: Actinic keratosis (AK)

Clinical formulation:

Table 2 Composition of Imiquimod 3.75% Topical Cream.

Name of Ingredient	Quantity (% w/w)	Reference to Standards	Function
Imiquimod	3.75	In-house Monograph	Active Drug Substance
Isostearic acid (b) (4)	(b) (4)		
Benzyl alcohol			
Cetyl alcohol			
Stearyl alcohol			
White Petrolatum			
Polysorbate 60 (b) (4)			
Sorbitan Monostearate			
Glycerin			
Xanthan gum			
Methylparaben			
Propylparaben			
Purified water			
Total	100.00		

The components of the drug product are the same as those for the approved product Aldara™ Cream, 5% (imiquimod). The Zyclara cream 3.75% differs only in the reduction of the concentrations of the active ingredient (imiquimod) from 5% to 3.75%, the (b) (4) of isostearic acid from (b) (4) and the (b) (4) in water content from (b) (4)

Route of administration: Topical

Proposed use:

Zyclara Cream (imiquimod 3.75%) should be applied once daily before bedtime to the skin of the affected area (entire face or balding scalp) for two 2-week treatment cycles separated by a 2-week no-treatment period. Zyclara Cream should be applied as a thin film to the entire treatment area and rubbed in until the cream is no longer visible. Up to 2 packets of Zyclara Cream may be applied to the treatment area at each application. Zyclara Cream should be left on the skin for approximately 8 hours, then the cream should be removed by washing the area with mild soap and water. Zyclara Cream is supplied in single-use packets, each of which contains 250 mg of the cream (equivalent to 9.4 mg of imiquimod).

Background:

Adara™ cream (imiquimod 5%), was previously approved for the treatment of external genital warts, actinic keratosis and superficial basal carcinoma (NDA 20-723). Aldara cream elicited a severe enough dermal irritation response that limited its clinical use to either a 2X/week, 3X/week or 5X/week treatment regimen (dependent on the indication). The sponsor intends to develop lower concentrations of imiquimod cream (3.75%) for the treatment of actinic keratosis but using a daily treatment regimen (applied daily for two 2-week treatment cycles separated by a 2-week no treatment period). The sponsor anticipates that the lower concentrations of imiquimod cream will be better tolerated to allow use of a daily treatment regimen and may allow reduced treatment duration. Under NDA 20-723, Aldara 5% cream was approved for a treatment regimen of 2X/week for 16 weeks for the treatment of actinic keratosis. The proposed frequency of administration is greater for the 3.75% imiquimod cream formulation compared to Aldara 5% cream. However, the total duration of treatment is less for the 3.75% imiquimod cream formulation compared to Aldara 5% cream.

A guidance meeting was conducted with the sponsor on July 27, 2007 to discuss the development of (b) (4) 3.75% imiquimod cream formulations for the treatment of (b) (4) , actinic keratosis (b) (4). After the review (by Dr. Barbara Hill) of nonclinical information available for Aldara (imiquimod) cream, 5%, it was determined that additional nonclinical toxicology studies would not be needed to support the safety of the (b) (4) of imiquimod cream (3.75% (b) (4) A pre-NDA meeting was conducted with the sponsor on Oct 29, 2008. The pharmacology/toxicology comments for the sponsor were: "It is acceptable for you to cross-reference the nonclinical studies contained in NDA 20-723 [Aldara (imiquimod) cream, 5%] to support the supplemental NDA submission for 3.75% imiquimod cream…". The sponsor has conducted four Phase 3 clinical studies with 2

investigational formulations (2.5% and 3.75% imiquimod creams) and one pharmacokinetic study with the 3.75% formulation of imiquimod cream in AK patients.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: None. The sponsor cross-references the nonclinical studies contained in NDA 20-723 [Aldara (imiquimod) Cream, 5%] to support this NDA submission. A summary of the nonclinical studies is provided in this NDA submission.

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Imiquimod is an immune response modifier that acts on the immune system by stimulating monocytes/macrophages and dendritic cells to produce interferon-α (INF-α) and other cytokines. Imiquimod is a human Toll-like receptor 7 (TLR7) agonist. Activation of TLRs is a critical step for the initiation of innate and adaptive immunity. The primary mechanism of action for imiquimod appears to be through the induction of the cytokine INF-α at the treatment site. Other cytokines and related molecules which are induced directly or indirectly following imiquimod treatment and may play a role in its pharmacologic action include tumor necrosis factor (TNF), interleukins (specifically IL-1, IL-2, IL-6 and IL-10), IL-1 receptor antagonist (IL-IRA), granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage inflammatory protein-1α and -1β (MIP-1α and MIP-1β), and monocyte chemotactic protein-1 (MCP-1). Two imiquimod metabolites, S-26704 (4-amino- α,α -dimethyl-H-imidazo [4,5-c] quinolin-1 ethanol) and S-27700 (4-amino-b-methyl-1H-imidazo [4,5-c] quinolin-1-propanol) are also pharmacologically active and induce cytokine production.

2.6.2.2 Primary pharmacodynamics:

refer to the brief summary above.

2.6.2.3 Secondary pharmacodynamics:

N/A

2.6.2.4 Safety pharmacology

Imiquimod belongs to the chemical class of substances known as imidazoquinolinamines. Although imiquimod resembles a nucleoside analog, its structure differs in several respects and does not function like a nucleoside analog. [^{14}C]-Imiquimod was not incorporated into cellular macromolecules and no effect on RNA or protein synthesis was noted *in vitro* at concentrations of 10 μg/ml. Imiquimod had no effect on the activities of the following enzymes: thymidine kinase, DNA polymerase, adenosine deaminase, xanthine oxidase, purine nucleoside phosphorylase or S-adenosylhomocysteine hydrolase. Imiquimod enhanced 2',5'-AS activity in guinea pig mononuclear cells. Imiquimod (≤ 10 μM) demonstrated slight inhibition of adenosine-2 binding in the NovaScreen receptor assay.

Intravenous doses of 0.5 to 5.0 mg/kg imiquimod produced cardiac stimulation, central nervous system stimulation and some evidence of autonomic nervous system inhibition in dogs. Stimulation of isolated guinea pig myocardium was observed at concentrations of 0.1 to 5.0 μg/ml. Tachyphylaxis was observed in isolated guinea pig myocardium after repeated exposure to imiquimod.

Imiquimod did not demonstrate any effects on inflammation or contact hypersensitivity in the various models except for one. A moderate inhibition of carrageenan-induced paw edema was noted in rats. Evidence of local anesthetic effect (sciatic nerve blockage) was observed in mice, but no analgesic effect was observed in the hotplate assay. Imiquimod demonstrated moderate hypothermia-induction when given intraperitoneally to mice. This effect was not observed after oral dosing in mice. Imiquimod produced a slight to moderate decrease in locomotor activity in mice and a slight increase in sleeptime, but had no effect on hexobarbital induced sleeptime. Other imiquimod effects included: slight urinary retention (rats), inhibition of antigen-induced bronchoconstriction (guinea pigs), moderate to marked inhibition of agonist induced tracheal contractions (guinea pig tracheal strips) and reversal or prevention of Sephadex particle-induced pulmonary hypersensitivity (rats). Diazepam was an effective antidote for lethal doses of imiquimod if given prior to administration of imiquimod in mice.

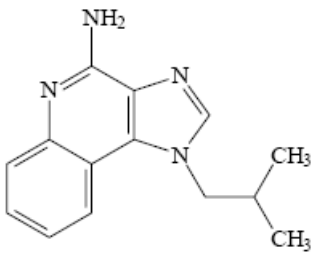
2.6.2.5 Pharmacodynamic drug interactions: N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY: N/A

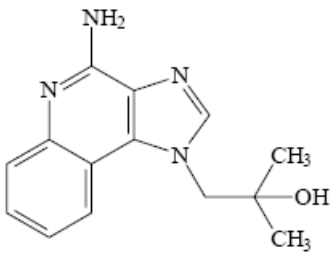
2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

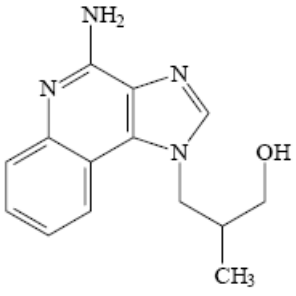
The pharmacokinetics and metabolism of imiquimod have been investigated to varying degrees in a wide range of animal models (mice, rats, guinea pigs, rabbits, dogs and monkeys) after intravenous, oral, subcutaneous, topical or intravenous administration. Concentrations of imiquimod and two of its metabolites, S-26704 and S-27700, have been measured in the biological fluids (e.g., serum, urine and bile) of animals using liquid chromatography and liquid chromatography-mass spectroscopy methods.



Imiquimod



S-26704



S-27700

The absolute oral bioavailability of [^{14}C]-imiquimod in rats was ~50% when measured as total radiolabel. However, the oral bioavailability of the parent drug is essentially zero due to extensive first-pass metabolism of imiquimod in rats. There was some evidence that oral bioavailability was dose-dependent, especially in rabbits. The absolute oral bioavailability of imiquimod was ~10% in monkeys, but the bioavailability of the radiolabel was much higher (77-100%). The molecular structure of < 6% of the absorbed radiolabel was identified in rats and rabbits. The principal identified metabolite in monkeys appears to be the hydroxylated, pharmacologically active product S-26704. Numerous other metabolites and conjugated products have been identified for imiquimod.

The results of radiomonitored TLC and LC analyses of urine collected from rats, rabbits, monkeys and guinea pigs after oral doses of [^{14}C]imiquimod indicated that metabolism of imiquimod was extensive, resulting in more than a dozen phase I and phase II metabolites in these species. The metabolite profiles for these species are qualitatively similar and consistent with metabolites identified in the urine of human subjects after oral doses of imiquimod. Very little unchanged drug was excreted in the urine of most animal species, usually less than 3% of the dose after intravenous dosing and even less after oral administration. Phase I biotransformation pathways for imiquimod are primarily characterized by hydroxylation at a variety of sites on the benzyl ring and at 2 sites on the 2-methylproply side chain. (b) (4) (b) (4) (b) (4). Most of the phase I metabolites appear to form glucuronide or sulfate conjugates, which are subsequently excreted in urine and bile. The chemical structures of the metabolites identified in the urine of laboratory animals and human subjects after dosing with imiquimod are consistent with the metabolites identified in the incubates of human hepatic microsomes. The chemical structures of metabolites produced in *in vitro* incubations of [^{14}C]imiquimod in the presence of human liver microsomes were determined by analyzing the incubation samples using LC-MS methods. All *in vitro* metabolite formation was microsome and NADPH-dependent. Eight phase I metabolites were identified in these studies.

Imiquimod-derived radiolabel distributes rapidly into most tissues, with concentrations usually less than or equal to circulating levels and highest tissue concentrations usually observed at ~3 hours after oral dosing. Apparently, imiquimod radiolabel has a particular affinity for pigments in the eye and skin. Although imiquimod radiolabel is cleared fairly rapidly from most tissues (radiolabel undetectable in most tissues at 24 hours), prolonged residence times were observed in pigmented tissues (eye and skin), liver and kidneys. There was some evidence of accumulation following repeat exposure at high doses. Fetal tissue exposure was demonstrated following intravenous administration of [^{14}C]imiquimod to pregnant rabbits. Fetus to maternal serum concentration ratios were consistently < 1 and elimination of radiolabel was essentially complete within 24 hours.

Elimination of imiquimod radiolabel is rapid and essentially complete by 72 hours after oral or parenteral administration. Topical application results in an apparent prolongation of systemic exposure. Urinary excretion of the radiolabel occurs most extensively within six hours after oral administration. Fecal elimination is most extensive between 6 and 24 hours after oral administration. Total recovery of the radiolabel in urine ranged from 27% – 49% after oral

dosing in rats. Radiochromatographic analysis of urine samples demonstrated numerous metabolites, consistent with extensive biotransformation. The apparent number of metabolites was increased following treatment of urine samples with β-glucuronidase, indicated the presence of glucuronide-conjugated metabolites.

Topical administration in guinea pigs of the imiquimod 5% cream resulted in a somewhat altered pattern of pharmacokinetics. Systemic exposure was somewhat prolonged with urinary excretion of the radiolabel observed up to 8 days after a single topical exposure. Trace amounts of parent drug were observed in serum samples. This was also observed following parenteral administration but not consistently after oral administration. There was no significant evidence that topical exposure resulted in altered biotransformation as compared to other routes of administration. Repeated topical administration in rats resulted in apparently negligible systemic exposure. The concentrations of parent drug and the two major metabolites (S-26704 and S-27700) were measured in these studies.

2.6.4.2 Methods of Analysis: liquid chromatography (LC) and liquid chromatography-mass spectroscopy (LC-MS) methods

2.6.4.3 Absorption: refer to the brief summary above.

2.6.4.4 Distribution: refer to the brief summary above.

2.6.4.5 Metabolism: refer to the brief summary above.

2.6.4.6 Excretion: refer to the brief summary above.

2.6.4.7 Pharmacokinetic drug interactions: N/A

2.6.4.8 Other Pharmacokinetic Studies

Clinical pharmacokinetic study brief summary:

The sponsor has conducted a clinical pharmacokinetic study under maximal use conditions of imiquimod 3.75% cream in AK patients (Study# GW01-0706). Two packets (500 mg of the drug product) were applied daily to the entire face or balding scalp of 19 AK patients for 3 weeks. Blood samples to determine the concentrations of imiquimod and its two metabolites combined (S-26704 and S-27700) were obtained at 9 time points on Days 1 and 21 and once at 48 and 72 hours after the last dose. The study has been reviewed by the clinical pharmacology reviewer (Dr. Dennis Bashaw) and Dr. Bashaw determined that this study was conducted under maximal use conditions (with the longest continuous duration of daily treatment - 3 weeks, with the largest product volume - 2 full packets, over a surface area estimated as approximately 200 cm^2 and in subjects with more severe disease - ≥ 10 AK lesions).

The pharmacokinetic parameters derived from this study are listed in the following table:

		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-24)}$ (ng.hr/mL)	$T_{1/2}$ (hr)
Day 1	Mean	0.136	9.772	1.831	19.818
	Max	0.275	24.030	3.601	33.930
Day 21*	Mean	0.315	7.281	5.841	29.260
	Max	0.588	16.000	11.800	84.059

*with subject 001-608

(b) (4)

Summary of toxicokinetic data available for carcinogenicity studies:

1. Toxicokinetic data for oral rat carcinogenicity study

(b) (4)

3 pages of draft labeling have been withheld in full immediately following this page as B4 CCI/TS

(b) (4)

2.6.4.9 Discussion and Conclusions

No additional nonclinical pharmacokinetic studies are recommended at this time.

2.6.4.10 Tables and figures to include comparative TK summary: N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY: N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Acute systemic toxicology summary:

Acute systemic toxicity studies were conducted in mice, rats and monkeys using either oral, intraperitoneal, subcutaneous or intravenous administration. Oral lethal doses ranged from 200 mg/kg in Cynomolgus monkeys to 1665 mg/kg in rats. Intravenous lethal doses ranged from 6 – 8 mg/kg. Intraperitoneal lethal doses were 763 mg/kg in rats and 879 mg/kg in mice. The subcutaneous lethal dose in rats was 20 mg/kg. Symptoms observed in acute toxicity studies included lethargy, hypoactivity, dyspnea, salivation (especially in rats), emesis (in monkeys), and convulsions, especially at lethal doses. Necropsy of animals that died in acute toxicity studies demonstrated evidence of gastric and intestinal hemorrhage, pale kidneys, and/or hyperemic lungs.

Repeat dose oral toxicology summary:

Repeat dose oral toxicology studies were conducted in rats and monkeys. Most of the adverse effects noted in the 1 and 6 month oral toxicity studies conducted in rats and monkeys at doses up to 30 and 20 mg/kg/day, respectively, could be attributed to imiquimod's pharmacological effects. These effects included lymph node and spleen hyperplasia with increases in mature T and B cells and increased numbers of plastocytes and immunoblasts. Splenomegaly and enlarged lymph nodes were observed at necropsy in high dose groups. Monocyte/macrophage infiltration was observed in various tissues including the lung, liver, kidney, leptomeninges, thyroid and bone marrow. Kupffer cell hyperplasia was also commonly observed in these studies.

Evidence of immune system exhaustion with decreased germinal center activity and atrophy in lymphoid organs was observed in the 6 month studies. Opportunistic infections, such as purulent gingivitis in monkeys, bacterial endocardiditis in rats and monkeys and pyelonephritis/prostatis in rats, developed in some high dose group animals in the 6 month

studies. Bone marrow failure, anemia and thrombocytopenia were commonly noted in the 6 month studies. Increases in monocytes and plasmocytes in bone marrow usually accompanied these effects. Increases in circulating white cells with shifts in lymphocyte populations (e.g., increased T-helper cells, decreased T-suppressor cells and B-cells) were commonly noted in the 6 month studies. Other commonly observed clinical signs included increased production of acute-phase proteins with increased serum globulins and decreased albumin. Decreases in body weight gain and food consumption were seen in 6 month studies, especially in monkeys. Adverse effects appeared to be reversible with cessation of treatment in low and mid dose animals. However, immune suppression persisted (e.g., bone marrow failure) in some high dose animals. Pilot studies demonstrated that twice-a-week dosing was better tolerated than daily dosing.

Dermal toxicology summary:

Dermal toxicology studies were conducted in rabbits, mice and rats. Single dermal doses up to 5 g/kg imiquimod 5% cream produced no apparent systemic toxicity in rabbits. A four month dermal toxicology study was conducted in mice with doses of 2.5, 15 and 75 mg/kg/dose applied 3 times/week. Mild to moderate skin irritation was noted in low dose animals. Severe skin irritation with scabbing and induration was noted in mid and high dose groups. Systemic effects included 6/10 and 9/10 deaths attributed to anemia in the mid and high dose groups, respectively. The systemic effects were similar to those observed following oral administration of imiquimod in mice.

A four week dermal toxicology study was conducted in rats with doses of 1, 2 or 5 mg/kg/dose applied 3 times/week. Moderate to severe skin irritation with erythema and edema were noted in treated rats. Evidence of systemic effects, increased spleen weights and reduced body weight gains, was observed in all dose groups. A four month dermal toxicology study was conducted in rats with doses of 0.5, 1 and 2.5 mg/kg/dose applied three times/week. The same adverse effects noted in the 4 week study were also noted in the four month study. In addition, clinical pathology signs (decreased serum protein) were noted in the four month study. Histopathology analysis failed to demonstrate that adverse effects in this study were accompanied by evidence of immune stimulation. A NOAEL could not be established in this study.

Genetic toxicology:

The following genetic toxicology information is contained in the Aldara cream label.

Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five *in vitro* genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three *in vivo* genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test).

In the submission, a new impurity, (b) (4), was identified during stability studies. The structure of (b) (4)

(b) (4)

Computational toxicology analysis using MultiCASE MC4PC and MDL-QSAR models (from CDER computational toxicology consult team, 06/15/2009, Appendix I) indicates that (b) (4) may have some genotoxic potential.

The sponsor states that (b) (4) is considered a degradation product noticed in the stability studies; its levels were not determined in the 5% imiquimod cream supplies used in any clinical or toxicology studies that were submitted to NDA 20-723. The sponsor also states that in *in vitro* metabolic studies of [^{14}C]-labeled imiquimod using human liver microsomes, (b) (4) derivatives represent 25% of all metabolites. However, the quantitative information of (b) (4) in the metabolic profiles of imiquimod in animals that were used in toxicology studies is not available. The quantitative information of (b) (4) in stability samples of 3.75% and 5% imiquimod creams is submitted to the NDA and reviewed by the CMC reviewer (Dr. Rajiv Agarwal). The information provided by Dr. Agarwal is summarized in the following table:

Batch No.	Imiquimod Concentration	Time point under storage conditions of 25°C/60% RH	Quantity of (b) (4)
GM7713	3.75%	39 weeks	(b) (4)
		12 months	
		18 months	
4331	5%	19 months	
		24 months	
CM1251	5%	18 months	
		24 months	

The proposed shelf-life of the drug product is 24 months. It appears that the quantity of (b) (4) in 3.75% cream is comparable to that in Aldara 5% cream. The maximum daily exposure to (b) (4) in 3.75% cream calculated based on stability data at 18 months of storage is: (b) (4). The maximum daily exposure to (b) (4) (b) (4) in Aldara 5% cream for the indication of AK calculated based on stability data at 24 months of storage is: (b) (4) According to the CDER guidance "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches", the acceptable qualification threshold for genotoxic and carcinogenic impurities to support marketing applications is (b) (4) which is below the calculated maximum daily exposure to (b) (4) contained in 3.75% cream (b) (4) However, after considering the following situations (1) the systemic exposure to (b) (4) after the topical application of the drug product is low (2) dermal carcinogenicity study of imiquimod cream showed negative results for the imiquimod-treated groups (see the section below) (3) the daily exposure to (b) (4)

(b) (4) in 3.75% cream is lower than that in Aldara 5% cream, the concern for genotoxicity potential of (b) (4) is not considered significant for the Zyclara 3.75% imiquimod cream.

Carcinogenicity:

The following carcinogenicity information is contained in the Aldara cream label.

In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2×/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2×/week in female rats (87× MRHD based on weekly AUC comparisons), 4 mg/kg administered 2×/week in male rats (75× MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7×/week to male and female rats (153× MRHD based on weekly AUC comparisons).

In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3×/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251× MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for Aldara Cream, minus the active moiety (imiquimod).

In a 52-week dermal photoco-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3×/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Aldara Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream.

Reviewer's comments: The multiples of Maximum Recommended Human Dose (MRHD) were calculated based on weekly AUC comparisons. Under the maximum use conditions of imiquimod cream, the maximum human AUC value of 82.6 ng.hr/mL per week for 3.75% cream is 10.59 fold greater than the maximum human AUC values of 7.8 ng.hr/mL per week for 5% cream, which was used previously for the calculation of multiples of MRHD in the carcinogenicity studies in NDA 20723. Therefore, for this NDA, the multiples of MRHD in the carcinogenicity studies will be (b) (4)

Reproductive toxicology:

The following reproductive toxicology information is contained in the Aldara cream label. Aldara cream is a Pregnancy Category C drug.

Daily oral administration of imiquimod to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87× MRHD based on AUC comparisons.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5, and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577× MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98× MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1, and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5× MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407× MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87× MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87× MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41× MRHD based on AUC comparisons).

Reviewer's comments: For the multiples of MRHD that were calculated based on daily AUC comparison, the multiples of MRHD for imiquimod 3.75% cream will change to 1/3.03 (0.33) fold of the previous multiples in the Aldara label. For the multiples of MRHD that were calculated based on daily BSA value, the multiples of MRHD for imiquimod 3.75% cream will change to (b) (4)

Special toxicology:

Imiquimod 5% cream was slightly irritating to rabbit skin after single dose administration. Repeated application of imiquimod 5% cream for 10 days resulted in no evidence of cumulative irritation or gross adverse systemic effects. Aged imiquimod creams (containing ~5% benzyl isostearate) were not more irritating than fresh cream formulations. Ocular irritation studies in rabbits did not demonstrate significant irritation after administration of imiquimod 5% cream.

Vaginal irritation studies in rats and rabbits at doses of 6 and 30 mg/kg/dose imiquimod resulted in evidence of edema associated with swollen vulvas in rats and minimal to mild irritation in rabbits. Histological examinations demonstrated scattered foci of mononuclear cells in rat vaginal epithelia. Occasionally mixed inflammatory infiltrates from rabbit cervical and vaginal tissues were noted in these studies. Vaginal studies in rats demonstrated significantly higher systemic exposure to imiquimod when compared to dermal studies conducted in rats.

Sensitization studies were conducted with imiquimod 5% cream in albino Hartley guinea pigs. Imiquimod was not a sensitizer in the guinea pig maximization test under the conditions of these studies.

Clinical dermal safety studies including a cumulative irritation study, a sensitization study, two photoirritation studies and a photoallergenicity study have been conducted with Aldara cream. Aldara cream demonstrated an absorption peak in the 290 – 320 nm UVB range. The medical officer, Dr. Milena Lolic, informed me that the sponsor have conducted two clinical photoirritation studies with Aldara cream after exposure to UVA/Visible light and UVB, respectively (the study for UVB was conducted as a PMC to approval for AK indication). Dr. Lolic also informed me that clinical dermal safety studies are not required for the development of 3.75% imiquimod cream because the new products are identical to the Aldara 5% cream except for the (b) (4) in the concentrations of imiquimod and isostearic acid and the corresponding (b) (4) in water concentrations (also refer to meeting minutes on 11/28/2007 for IND 49,480).

2.6.6.2 Single-dose toxicity – refer to the summary above.

2.6.6.3 Repeat-dose toxicity – refer to the summary above.

2.6.6.4 Genetic toxicology – refer to the summary above.

2.6.6.5 Carcinogenicity – refer to the summary above.

2.6.6.6 Reproductive and developmental toxicology – refer to the summary above.

2.6.6.7 Local tolerance – refer to the summary above.

2.6.6.8 Special toxicology studies – refer to the summary above.

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY – N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for oral imiquimod and imiquimod cream, NDA 22-483 [Zyclara (imiquimod) Cream, 3.75%] for the treatment of actinic keratosis is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the Zyclara cream label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-483, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the Zyclara cream label.

Suggested labeling:

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Zyclara cream label reproduced below.

(b) (4)

4 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM

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

/s/

JIANYONG WANG
08/03/2009

BARBARA A HILL
08/03/2009
I concur