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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: ZYCLARA (imiquimod) Cream 3.75%
Indication: External genital and perianal warts/condyloma
acuminata
Applicant: Graceway Pharmaceuticals
Review Division: Dermatology and Dental Products
Reviewer: Jianyong Wang
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

NDA 201153 for drug product Zyclara Cream (imiquimod 3.75%) is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.1.3 are incorporated into the Zyclara Cream label.

1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

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

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. ZYCLARA Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Note: The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. The animal multiples of human exposure were based on weekly dose comparisons for the carcinogenicity studies described in this label. For the animal multiple of human exposure ratios presented in this label, the Maximum Recommended Human Dose (MRHD) was set at 2 packets (500 mg cream) per treatment of actinic keratosis with ZYCLARA Cream (imiquimod 3.75%, 18.75 mg imiquimod) for BSA comparison. The maximum human AUC value obtained in the treatment of external genital and perianal warts was higher than that obtained in the treatment of actinic keratosis and was used in the calculation of animal multiples of MRHD that were based on AUC comparison.

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 (163 (b) (4) X 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 (28^{(b)(4)} 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 (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (115^{(b)(4)}X 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 (25^{(b)(4)}X 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 (25^{(b)(4)}X 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 (12^{(b)(4)}X MRHD based on AUC comparisons).

Reviewer's comments: Imiquimod does not have an established pharmacologic class, based on the following: (1) the mechanism of action (MOA) for imiquimod is unknown and (2) the physiologic effect (PE) and chemical structure (CS) of imiquimod are not clinically meaningful. Therefore, a pharmacologic class is not designated for imiquimod at this time and such recommendation received clinical concurrence (from Drs. Milena Lolic and Jill Lindstrom).

12.1 Mechanism of Action

The mechanism of action of ZYCLARA Cream in treating AK and EGW lesions is unknown.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/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 2X/week in female rats (7.1^{(b)(4)}X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (6.1^{(b)(4)}X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (12^{(b)(4)}X 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 3X/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 (21^(b)₍₄₎X 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.

In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with 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.

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).

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 25^(b)₍₄₎X MRHD based on AUC comparisons.

1.2 Brief Discussion 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 (cytokine inducer).
- 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 photocarcinogenicity study.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

99011-02-6

2.1.2 Generic Name

Imiquimod 3.75% cream

2.1.3 Code Name

R-837, S-26308

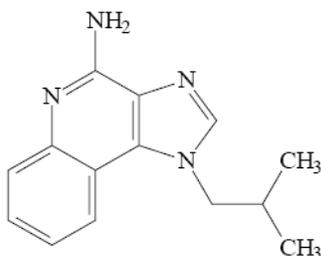
2.1.4 Chemical Name

1-(2-methylpropyl)-1 H-imidazo[4,5-c]quinoline-4-amine

2.1.5 Molecular Formula/Molecular Weight

C₁₄H₁₆N₄ / 240.3

2.1.6 Structure



2.1.7 Pharmacologic class

Immune modulator (cytokine inducer)

Reviewer's comments: A pharmacologic class is not designated for imiquimod in the drug label at this time (see comments in Section 1.1.3). "Immune modulator" and "cytokine inducer" are used here to describe the pharmacological effects of imiquimod. However, the two names appear to be too broad and unspecific and they are not considered appropriate for the name of an established pharmacologic class in the drug label.

2.2 Relevant IND/s, NDA/s, and DMF/s

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

- 9) IND (b) (4)
- 10) IND (b) (4)
- 11) IND (b) (4)
- 12) IND (b) (4)
- 13) NDA 20-723 [Aldara (imiquimod) 5% cream; external genital/perianal warts; DDDP; approved 2-27-97]
- 14) NDA 22-483 [Zyclara (imiquimod) 3.75% cream; actinic keratosis; DDDP; approved 3-25-10]

2.3 Clinical Formulation

2.3.1 Drug Formulation

This drug formulation has been approved to treat actinic keratosis under NDA 22483.

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 (Vegetable source)	(b) (4)	In-house Monograph	(b) (4)
Benzyl alcohol		USP-NF / Ph.Eur.	
Cetyl alcohol		USP-NF / Ph.Eur.	
Stearyl alcohol		USP-NF / Ph.Eur.	
White Petrolatum		USP-NF / White Soft Paraffin Ph.Eur.	
Polysorbate 60	(b) (4)	USP-NF / Ph.Eur.	
Sorbitan Monostearate		USP-NF / Ph.Eur.	
Glycerin		USP-NF / Glycerol Ph.Eur.	
Xanthan gum		USP-NF / Ph.Eur.	
Methylparaben		USP-NF / Methyl Parahydroxybenzoate Ph. Eur.	
Propylparaben		USP-NF / Propyl Parahydroxybenzoate Ph. Eur.	
Purified water		USP-NF / Ph.Eur.	
Total	100.00		

2.3.2 Comments on Novel Excipients

None.

2.3.3 Comments on Impurities/Degradants of Concern

An impurity, (b) (4), was identified in the stability studies submitted to NDA 22483. Computational toxicology analysis indicated that (b) (4) may have some genotoxic potential. The maximum daily exposure to (b) (4) in Zyclara Cream for the EGW indication calculated based on stability data is: (b) (4), which is half of the maximum daily exposure to (b) (4) in Zyclara Cream for the AK indication. Per the CDER guidance, the acceptable qualification threshold for genotoxic and carcinogenic impurities to support marketing applications is 1.5 µg, which is below the calculated maximum daily exposure to (b) (4) for the EGW indication. 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) in Zyclara cream is lower than that in Aldara 5% cream, the concern for genotoxicity potential of (b) (4) is not considered significant for the Zyclara Cream (refer to the nonclinical review for NDA 22483 entered into DARRTS on 8/3/09).

2.4 Proposed Clinical Population and Dosing Regimen

Clinical population: patients 12 years or older with external genital and perianal warts/condyloma acuminata.

Dosing Regimen: Once daily to the external genital/perianal warts until total clearance or up to 8 weeks.

2.5 Regulatory Background

Adara[®] cream (imiquimod 5%), was previously approved for the treatment of external genital warts (EGW), actinic keratosis (AK) and superficial basal carcinoma (SBC) (NDA 20723). Aldara cream elicited a severe enough dermal irritation response that limited its clinical use to either a 2X/week, 3X/week or a 5X/week treatment regimen (dependent on the indication). Under NDA 22483, the sponsor developed a lower concentration (3.75%) of imiquimod cream, Zyclara[®] cream, for the treatment of AK, using a daily treatment regimen (applied daily for two 2-week treatment cycles separated by a 2-week no treatment period). NDA 22483 was approved by the Agency on 03/25/2010. Under this NDA the sponsor intends to develop Zyclara[®] cream for the treatment external genital and perianal warts/condyloma acuminata in patients 12 years or older, using a daily treatment regimen (applied daily until total clearance or up to 8 weeks). The approved treatment regimen of Adara[®] cream (imiquimod 5%) for the treatment of EGW is 3 times per week until total clearance or up to 16 weeks.

A preNDA meeting was held with the sponsor on 11/18/2009. The sponsor was informed that a comprehensive summary of nonclinical information with corresponding cross-reference information for the pivotal nonclinical studies contained in previous IND/NDAs should be provided in the NDA submission (a similar presentation of the nonclinical information in NDA 22483 will be acceptable for this NDA). Subsequently the sponsor submitted NDA 201153 for the Zyclara[®] cream product on 02/12/2010 (SDN 1). This NDA cross-references the nonclinical studies contained in NDA 20723 and includes a comprehensive summary of those nonclinical studies. All the studies have been reviewed previously by the Division. No additional nonclinical studies are recommended for Zyclara[®] cream, at this time. The sponsor submitted the revised labeling on 06/08/2010 (SDN 3).

If NDA 201153 is approved, there will be one single label for Zyclara[®] cream, which contains both AK and EGW indications.

3 Studies Submitted

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

The nonclinical review for NDA 22483 (entered into DARRTS on 08/03/2009).

4 Pharmacology

4.1 Primary Pharmacology

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-1RA), granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage inflammatory protein-1 α and -1 β (MIP-1 α and MIP-1 β), 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.

4.2 Secondary Pharmacology

None.

4.3 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. [¹⁴C]-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.

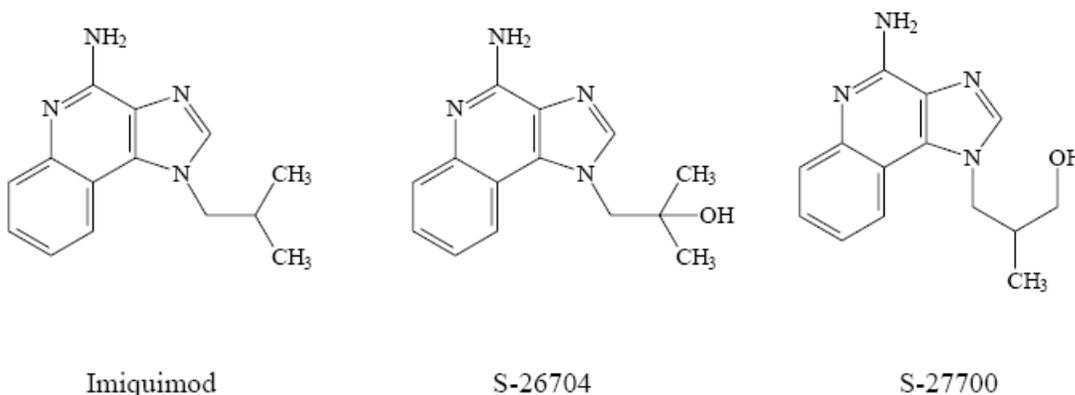
Intravenous doses of 0.5 to 5.0 mg/kg imiquimod produced cardiac stimulation, central nervous system stimulation and some evidence of autonomic nervous system inhibition in dogs. Stimulation of isolated guinea pig myocardium was observed at concentrations of 0.1 to 5.0 µg/ml. Tachyphylaxis was observed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

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

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. Liquid chromatography (LC) and liquid chromatography-mass spectroscopy (LC-MS) methods were used for analysis. 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.



The absolute oral bioavailability of [¹⁴C]-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 [¹⁴C]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-methylpropyl side chain. Also, N-oxide formation occurs on the primary nitrogen of the quinoline ring. 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 [¹⁴C]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 [¹⁴C]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.

Comparison to clinical PK parameters for the calculation of multiples of human exposure:

The sponsor has conducted a clinical PK study under anticipated maximal use conditions of imiquimod 3.75% cream in EGW patients (Study# GW01-0804). Dr. Dennis Bashaw, the clinical pharmacology reviewer, has determined that this 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 ≥ 100 mm² applied once daily applications of up to 1 packet of 3.75% imiquimod cream for 3 continuous weeks (21 days).

The major PK parameters derived from this study are listed in the following table (obtained from Dr. Bashaw's review):

			C _{max} (ng/ml)	T _{max} (hr)	AUC ₍₀₋₂₄₎ (ng.hr/ml)	T _{1/2} (hr)
Day 1	Male	Mean	0.210	12.257	3.237	13.103
		Max	0.434	16.000	6.165	32.595
	Female	Mean	0.386	8.000	4.771	11.537
		Max	1.022	12.000	11.453	24.575
Day 21	Male	Mean	0.426	11.019	6.790	25.677
		Max	0.692	16.000	11.536	53.990
	Female	Mean	0.597	5.400	6.474	18.010
		Max	1.632	12.000	13.735	25.337

The multiples of human exposure for the nonclinical toxicology studies contained in the label should be calculated based on the maximal use clinical conditions for Zyclara Cream. It is recommended that the maximum human AUC value of 13.7 ng.hr/ml per day be used for the calculation of the multiples of human exposure based on daily AUC data. It is recommended that the maximum human AUC value of 95.9 ng.hr/ml per week be used for the calculation of the multiples of human exposure based on weekly AUC data (13.7 ng.hr/ml per day \times 7 days per week = 95.9 ng.hr/ml per week).

When adequate AUC data are not available from nonclinical toxicology studies contained in the Zyclara Cream label, it is recommended that the multiple of human exposure calculations be based on body surface area (BSA) comparisons. The maximum human BSA value would be 5.79 mg/m²/day for the calculation of the multiples of human exposure based on daily BSA data for the EGW indication [1 packet/day \times 250 mg/packet \times 3.75% \div 60 kg = 0.16 mg/kg/day (5.79 mg/m²/day, using 1.62 m² for a 60 kg individual)]. The maximum human BSA value would be 40.51 mg/m²/week for the calculation of the multiples of human exposure based on weekly BSA data for the EGW indication [1 packet/day \times 250 mg/packet \times 3.75% \times 7 days/week \div 60 kg = 1.09 mg/kg/week (40.51 mg/m²/week)].

In the Zyclara Cream label for the AK indication, the maximum human AUC values of 11.8 ng.hr/ml per day and 82.6 ng.hr/ml per week were used for the calculation of multiples of human exposure based on daily and weekly AUC data, respectively. When adequate AUC data were not available, the maximum human BSA value of 11.57 mg/m²/day and 81.02 mg/m²/week were used for the calculation of multiples of human

exposure based on daily and weekly BSA data, respectively (2 packets/treatment, applied daily for two 2-week treatment cycles separated by a 2-week no treatment period). Therefore, for multiples of human exposure based on AUC comparison, the multiples for EGW indication will change to 0.86 fold ($11.8 \text{ ng}\cdot\text{hr}/\text{ml} \div 13.7 \text{ ng}\cdot\text{hr}/\text{ml} = 0.86$) of the multiples for AK indication; for multiples of human exposure based on BSA comparison, the multiples for EGW indication will change to 2 fold (2 packets/day vs. 1 packet/day) of the multiples for AK indication. Since there will be only one label to cover both AK and EGW indications, the lower multiples of human exposure from one of the two indications will be used in the description of nonclinical toxicology studies in the label.

For the reproductive toxicology and carcinogenicity studies in the Zyclara Cream label, the multiples of Maximum Recommended Human Dose (MRHD) that were based on AUC comparison will change to 0.86 fold of the previous multiples in the Zyclara Cream label. The multiples of MRHD that were based on BSA comparison will remain unchanged.

5.2 Toxicokinetics

Summary of toxicokinetic data available for carcinogenicity studies:

1. Toxicokinetic data for oral rat carcinogenicity study

Oral doses that mimicked the doses administered to rats in a two-year oral carcinogenicity study were orally (gavage) administered to rats (16/sex/group) for 8 weeks in the TK study. The Week 8 $\text{AUC}_{0-24 \text{ hr}}$ values for imiquimod and the two metabolites, S-26704 and S-27700 are provided in the following two tables. Only the Week 8 values are presented because it is anticipated that the Week 8 value would represent a steady state value. The Week 8 $\text{AUC}_{0-24 \text{ hr}}$ values will be used for calculating multiples of human exposure for labeling purposes.

Males:

Dose (mg/kg)	Parameter	Imiquimod	S-26704	S-27700	Total/dose ^a	Total/week ^a
1 (2X/week)	C_{max} (ng/ml)	--	9.4	--	NA	NA
	$\text{AUC}_{0-24 \text{ hr}}$ (ng·hr/ml)	--	35	--	35	70
2 (2X/week)	C_{max} (ng/ml)	--	23	--	NA	NA
	$\text{AUC}_{0-24 \text{ hr}}$ (ng·hr/ml)	--	99	--	99	198
4 (2X/week)	C_{max} (ng/ml)	9.1	41	7.5	NA	NA
	$\text{AUC}_{0-24 \text{ hr}}$ (ng·hr/ml)	52	218	3.8	274	584
3 (Daily)	C_{max} (ng/ml)	12	28	--	NA	NA
	$\text{AUC}_{0-24 \text{ hr}}$ (ng·hr/ml)	30	151	--	181	1267

a – Imiquimod + S-26704 + S-27700

-- – below the level of quantification (<5 ng/ml)

NA – not applicable

Females:

Dose (mg/kg)	Parameter	Imiquimod	S-26704	S-27700	Total/dose ^a	Total/week ^a
2 (2X/week)	C _{max} (ng/ml)	--	20	--	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	--	55	--	55	110
4 (2X/week)	C _{max} (ng/ml)	9.9	55	--	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	14	202	--	216	432
6 (2X/week)	C _{max} (ng/ml)	21	76	--	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	36	303	--	339	678
3 (Daily)	C _{max} (ng/ml)	11	31	--	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	43	117	--	160	1120

a – Imiquimod + S-26704 + S-27700

-- – below the level of quantification (<5 ng/ml)

NA – not applicable

It appears that adequate systemic exposure was achieved at the doses used in the oral rat carcinogenicity study. Therefore, the multiples of human exposure for the oral rat carcinogenicity study can be calculated based on AUC comparisons based on the data obtained in the oral rat toxicokinetic study. The total/week AUC_{0-24 hr} value (represents Imiquimod + S-26704 + S-27700) will be used for calculation of multiples of human exposure for labeling purposes.

2. Toxicokinetic data for dermal mouse carcinogenicity study

Two topical doses that mimicked the low and high dose levels administered to mice in a two-year dermal carcinogenicity were administered to CD-1 mice (40/sex/group) for 2 weeks in the TK study. It would have been preferable if the sponsor would have dosed the animals for a longer duration (perhaps 4 weeks) because it is not clear if the pharmacokinetics would reach a plateau after 2 weeks of treatment. However, it has been decided that AUC data obtained from this study could be used to calculate the multiples of human exposure for the dermal mouse carcinogenicity study based on AUC comparisons for labeling purposes.

Analyte	Parameter	Low dose (0.03% imiquimod cream)			High dose (0.3% imiquimod cream)		
		Male	Female	M & F	Male	Female	M & F
Imiquimod	C _{max} (ng/ml)	37.9	12.5	24.5	47.6	34.5	36.3
	T _{max} (hr)	1	0.5	1	3	4	1
	AUC _(0-24 hr) (ng·hr/ml)	182	78	130	504	220	362
	AUC _(0-24 hr) (nmol·hr/ml)	0.757	0.325	0.541	2.10	0.916	1.51
S-26704/ S-27700	C _{max} (ng/ml)	5.2	4.7	5.0	35.0	45.6	38.1
	T _{max} (hr)	1	1	1	2	1	1
	AUC _(0-24 hr) (ng·hr/ml)	18.5	16.9	17.7	150	161	155
	AUC _(0-24 hr) (nmol·hr/ml)	0.0722	0.0659	0.0691	0.585	0.628	0.605
Imiquimod + S-26704/ S-27700	AUC _(0-24 hr) (ng·hr/ml)	201	95	148	654	381	517
	AUC _(0-24 hr) (nmol·hr/ml)	0.830	0.391	0.610	2.68	1.54	2.11

Summary of toxicokinetic data for reproductive and developmental toxicology studies:

A systemic embryofetal development study was performed in rats. Oral doses (via gavage) of 0, 1, 5 and 20 mg/kg/day (0, 6, 30 and 120 mg/m²/day) imiquimod were administered to pregnant female CD rats (25 females/dose group) on gestational Days 6 – 15. The NOEL for embryofetal toxicity and teratogenicity was identified as 5 mg/kg/day (30 mg/m²/day or 210 mg/m²/week). Fetal toxicity and teratogenicity were noted at the maternally toxic dose of 20 mg/kg/day. In the absence of appropriate nonclinical pharmacokinetic data, the multiples of human exposure will be calculated based on body surface area comparisons instead of AUC comparisons. However, the sponsor argued in the toxicokinetic data to support labeling submission that the results of 2X/week dosing and the daily dosing yielded the same toxicokinetic data. Therefore, the sponsor proposed that it would be appropriate to use the 2X/week dosing regimen used in the toxicokinetic study conducted to support the oral rat carcinogenicity study to support the daily dosing regimen used in the reproductive toxicology study. It appears that the total AUC_{0-24 hr} per dose is independent of the dosing regimen. The AUC_{0-24 hr} per dose value for the 3 mg/kg dose administered 7X/week falls between the 2 and 4 mg/kg doses administered 2X/week. It would be acceptable to use the AUC_{0-24 hr} per dose value for the 4 mg/kg/dose (216 ng·hr/ml) for calculating the multiples of human exposure based on AUC comparisons for the 5 mg/kg/day dose used in the oral rat embryofetal developmental study. Use of the pharmacokinetic data for the 4 mg/kg/dose for this calculation even though the actual dose was 5 mg/kg/day, would be acceptable since this will underestimate the animal to human dose ratio (i.e., the error would be on the side of caution).

A systemic embryofetal development study was performed in rabbits. Intravenous doses of 0, 0.5, 1.0 and 2.0 mg/kg/day (0, 6, 12 and 24 mg/m²/day) imiquimod were administered to pregnant female New Zealand white rabbits (20 females/dose group) on gestational Days 6 – 18. The NOEL for embryofetal toxicity and teratogenicity was identified as 2 mg/kg/day (24 mg/m²/day or 168 mg/m²/week), the highest dose tested in the study. In the absence of nonclinical pharmacokinetic data for the high dose group, the multiples of human exposure will be calculated based on body surface area comparisons for the high dose. However, pharmacokinetic data is available for the mid dose group in this study. A separate pharmacokinetic study was conducted in New Zealand White rabbits (Study# R-837-DM-45). An intravenous dose of 1.0 mg/kg/day [¹⁴C] imiquimod was administered to rabbits on gestational days 6 – 18. The pharmacokinetic data for the first dose (Dose 1) and the last dose (Dose 13) are listed in the following table:

Dose	Parameter	Imiquimod	S-26704	Total/dose ^a	Total/week ^a
Dose 1; 1 mg/kg	C _{max} (ng/ml)	176	13	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	1296	94	1390	9730
Dose 13; 1 mg/kg	C _{max} (ng/ml)	131	24	NA	NA
	AUC _{0-24 hr} (ng·hr/ml)	1512	77	1589	11123

a – Imiquimod + S-26704

NA – not applicable

It is acceptable to calculate the multiples of human exposure based on AUC data for the mid dose group (1589 ng.hr/ml per day) for labeling purpose.

A combined fertility and peri- and post-natal developmental study was performed in rats. Oral (via gavage) doses of 0, 1.5, 3 and 6 mg/kg/day (0, 9, 18 and 36 mg/m²/day) imiquimod were administered in this study. Males were treated for 70 days prior to mating and continued through mating. Females were treated for 14 days prior to mating and through parturition and lactation. The NOEL for teratogenicity was identified as 3 mg/kg/day imiquimod in the combined fertility and peri- and post-natal developmental study conducted in rats. Teratogenic effects were noted at a dose of 6 mg/kg/day. The NOEL for fertility and postnatal development was 6 mg/kg/day imiquimod in the combined fertility and peri and post-natal developmental study conducted in rats. The mid dose group used in this study is the same as the mid dose group that was used in the oral rat toxicokinetic study conducted to support the oral rat carcinogenicity study. The multiple of human exposure for the mid dose group (3 mg/kg/day) used in this study can be calculated based on AUC data obtained in the oral rat toxicokinetic study (160 ng.hr/ml per day). The sponsor argued in the toxicokinetic data to support labeling submission that the results of 2X/week dosing and the daily dosing yielded the same toxicokinetic data. Therefore, the sponsor proposed that it would be appropriate to use the 2X/week dosing regimen used in the toxicokinetic study conducted to support the oral rat carcinogenicity study for the 6 mg/kg/day dose used in the reproductive toxicology study. It appears that the total AUC_{0-24 hr} per dose is independent of the dosing regimen. The AUC_{0-24 hr} per dose value for the 3 mg/kg dose administered 7X/week falls between the 2 and 4 mg/kg doses administered 2X/week. It is acceptable

to use the $AUC_{0-24 \text{ hr}}$ per dose value for the 6 mg/kg/dose (339 ng.hr/ml) for calculating the multiples of human exposure based on AUC comparisons for the 6 mg/kg/day dose used in the oral rat combined fertility and peri- and postnatal developmental study.

6 General Toxicology

6.1 Single-Dose Toxicity

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.

6.2 Repeat-Dose Toxicity

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 plasmacytes 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 endocarditis in rats and monkeys and pyelonephritis/prostatitis 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 plasmacytes 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.

7 Genetic Toxicology

The following genetic toxicology information is contained in the Zyclara 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).”

No changes are recommended for the new Zyclara Cream label at this time.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Refer to the summary above.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Refer to the summary above.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Refer to the summary above.

7.4 Other Genetic Toxicity Studies

None.

8 Carcinogenicity

The following carcinogenicity information is contained in the Zyclara cream label:

“In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/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 2X/week in female rats (8.2X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (7.1X MRHD) based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats ((b) (4)X 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 3X/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 ((b) (4)X 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.

In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with 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.”

Per the discussion in Section 5.1, the animal multiples of MRHD need to be changed to 0.86 fold of the multiples in the previous Zyclara Cream label if the multiples were calculated based on AUC comparison (see Section 1.1.3 for the recommended labeling changes). No additional changes are recommended at this time.

9 Reproductive and Developmental Toxicology

The following reproductive and developmental toxicology information is contained in the Zyclara Cream label:

“Pregnancy Category C:

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 (b) (4)X 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 (190X 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 (b) (4)X 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 (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (134X 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 (b) (4)X 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 (b) (4)X 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 (b) (4)X MRHD based on AUC comparisons).”

Per the discussion in Section 5.1, the animal multiples of MRHD need to be changed to 0.86 fold of the multiples in the previous Zyclara Cream label if the multiples were calculated based on AUC comparison (see Section 1.1.3 for the recommended labeling changes). No additional changes are recommended at this time.

9.1 Fertility and Early Embryonic Development

Refer to the summary above.

9.2 Embryonic Fetal Development

Refer to the summary above.

9.3 Prenatal and Postnatal Development

Refer to the summary above.

10 Special Toxicology Studies

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 clinical reviewer concluded that clinical dermal safety studies are not required for the development of the 3.75% imiquimod cream (refer to the nonclinical review for NDA 22483 entered into DARRTS on 8/3/09).

11 Integrated Summary and Safety Evaluation

Adara Cream (imiquimod 5%) was previously approved under NDA 20723 for the treatment of EGW with a dosing regimen of 3 times per week until total clearance or up to 16 weeks. Zyclara Cream (imiquimod 3.75%) has been recently approved under NDA 22483 for the treatment of AK, with a dosing regimen of once daily for two 2-week treatment cycles separated by a 2-week no-treatment period. This NDA cross-references nonclinical information contained in previous IND/NDAs and no new nonclinical information is contained in this NDA. No additional nonclinical studies are needed for the approval of this NDA.

Based on the nonclinical data available for oral imiquimod and imiquimod cream, NDA 201153 [Zyclara (imiquimod) Cream, 3.75%] for the treatment of external genital and perianal warts/condyloma acuminata is approvable from a pharmacology/toxicology perspective, provided that the recommended changes in the label described in Section 1.1.3 are incorporated into the Zyclara Cream label.

12 Appendix/Attachments

None.

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
09/29/2010

BARBARA A HILL
09/29/2010
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201153 **Applicant:** Graceway pharmaceuticals, **Stamp Date: 2/8/2010**
Bristol, Tennessee

Drug Name: ZYCLARA **NDA/BLA Type: Original-Standard**
(imiquimod cream), 3.75%

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD NDA submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Summary information of the required studies is 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, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		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	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 applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Summary information of the required studies is submitted to this NDA; the study reports are referred to previous NDA/INDs.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	It is not applicable to this NDA.
11	Has the applicant addressed any abuse potential issues in the submission?		X	It is not applicable to this NDA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	This NDA is not to support a Rx to OTC switch.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A.

Jianyong Wang

3/24/2010

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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
03/31/2010

BARBARA A HILL
04/01/2010