CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-548

Name: Imiquimod Cream, 5%

Sponsor: Nycomed U.S., Inc.

Approval Date: February 25, 2010

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APPLICATION NUMBER:

ANDA 78-548

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APPLICATION NUMBER:

ANDA 78-548

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078548

Nycomed U.S., Inc.
Attention: Robert J. Anderson, Esq.
Vice President, Scientific Affairs
60 Baylis Road
P.O. Box 2006
Melville, NY 11747

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 16, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Imiquimod Cream, 5%.

Reference is also made to your amendments dated April 27 and October 2, 2007; January 22, February 13, March 31, June 12, July 25, August 15, August 22 and August 28, 2008; March 13, 2009; and January 20, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Imiquimod Cream, 5%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Aldara Cream, 5%, of Graceway Pharmaceuticals, LLC. (Graceway).

The RLD upon which you have based your ANDA, Graceway's Aldara Cream, 5%, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 4,689,338 (the '338 patent) and 5,238,944 (the '944 patent) are scheduled to expire (with pediatric exclusivity added) on February 25, 2010, and February 24, 2011, respectively.

With respect to the ‘944 patent, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that this patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Imiquimod Cream, 5%, under this ANDA. You have notified the agency that Nycomed U.S., Inc. (Nycomed) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the ‘944 patent was brought against Nycomed within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

We note that the ‘338 patent has expired.

With respect to 180-day generic drug exclusivity, we note that Nycomed was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '944 patent. Therefore, with this approval, Nycomed is eligible for 180 days of generic drug exclusivity for Imiquimod Cream, 5%. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins. The agency notes that Nycomed failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. However, the agency has determined that the failure to obtain tentative approval within 30 months was caused by the agency’s ongoing review of the requirements for approval of Imiquimod Cream, 5%, and therefore Nycomed did not forfeit eligibility for 180-day generic drug exclusivity. See section 505(j)(5)(D)(i)(IV) of the Act.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence - SPL for Approved ANDA 078548".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78548	ORIG-1	NYCOMED US INC	IMIQUIMOD

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

/s/

ROBERT L WEST
02/25/2010
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

LABELING

fougera®

NDC 0168-0432-26
NET WT. 0.25 g

℞ only

IMIQUIMOD CREAM 5%

Contains 1 Application
Discard Unused Portion

For Dermatologic Use Only
Not for Ophthalmic Use

tear here
foilpac®

See Package Insert for Dosage Information.
Store at 4°-25°C (39°-77°). Avoid Freezing.

E. FOUGERA & CO.
A division of Nycomed US Inc.
Melville, New York 11747

FP5386
R1/08

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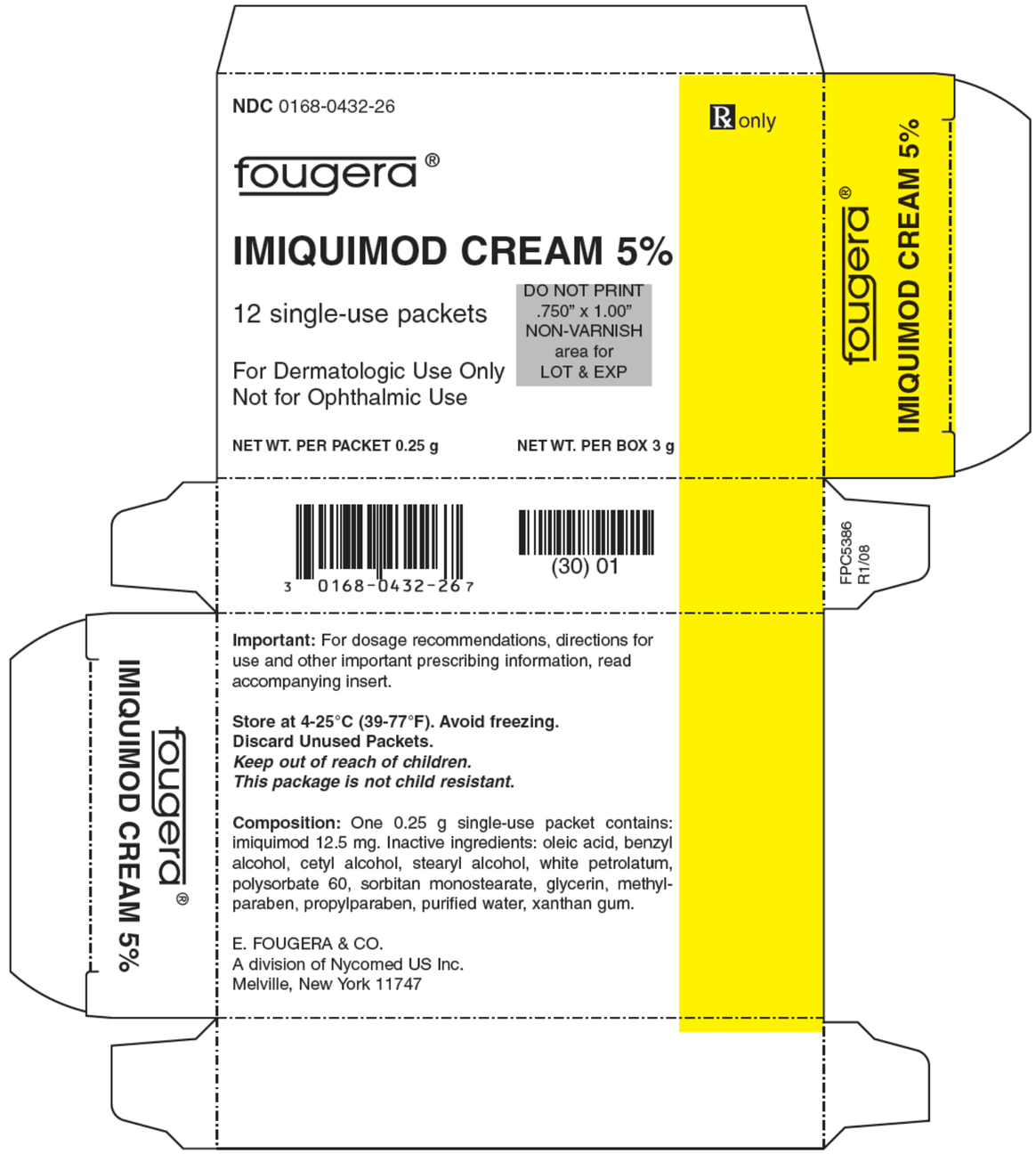
NDC 0168-0432-26
fougera®
IMIQUIMOD CREAM 5%
12 single-use packets
DO NOT PRINT
.750" x 1.00"
NON-VARNISH
area for
LOT & EXP
For Dermatologic Use Only
Not for Ophthalmic Use
NET WT. PER PACKET 0.25 g
NET WT. PER BOX 3 g
℞ only
3 0168-0432-26 7
(30) 01
fougera®
IMIQUIMOD CREAM 5%
FPC5386
R1/08
Important: For dosage recommendations, directions for use and other important prescribing information, read accompanying insert.
Store at 4-25°C (39-77°F). Avoid freezing.
Discard Unused Packets.
Keep out of reach of children.
This package is not child resistant.
Composition: One 0.25 g single-use packet contains: imiquimod 12.5 mg. Inactive ingredients: oleic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, methylparaben, propylparaben, purified water, xanthan gum.
E. FOUGERA & CO.
A division of Nycomed US Inc.
Melville, New York 11747
fougera®
IMIQUIMOD CREAM 5%

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imiquimod Cream safely and effectively. See full prescribing information for Imiquimod Cream.
For topical use only
Initial U.S. Approval _____

----------INDICATIONS AND USAGE----------
Imiquimod Cream is indicated for the topical treatment of:
- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults (1.1)
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured (1.2)
- External genital and perianal warts/condyloma acuminata in patients 12 years old or older (1.3)

Limitations of use: Efficacy was not demonstrated for molluscum contagiosum in children aged 2-12 (1.4, 8.4)

----------DOSAGE AND ADMINISTRATION----------
Imiquimod Cream is not for oral, ophthalmic, or intravaginal use. (2)
- Actinic keratosis: 2 times per week for a full 16 weeks (2.1)
- Superficial basal cell carcinoma: 5 times per week for a full 6 weeks (2.2)
- External genital warts (EGW): 3 times per week until total clearance or maximum of 16 weeks (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Imiquimod Cream 5% is supplied in single-use packets (12 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Intense local inflammatory reactions can occur (e.g., skin weeping, erosion). Dosing interruption may be required (2, 5.1, 6)
- Flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors may occur. Dosing interruption may be required (2, 5.2, 6)
- Avoid exposure to sunlight and sunlamps. Wear sunscreen daily (5.3).
- Safety and efficacy have not been established for repeat courses of treatment to the same area for AK. (5.4)
- Imiquimod Cream is not recommended for treatment of BCC subtypes other than the superficial variant, i.e., sBCC. (5.5)
- Treatment of urethral, intra-vaginal, cervical, rectal or intra-anal viral disease is not recommended. (5.6)
- Safety and efficacy in immunosuppressed patients have not been established (1.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >28%) are application site reactions or local skin reactions: itching, burning, erythema, flaking/scaling/dryness, scabbing/crusting, edema, induration, excoriation, erosion, ulceration. Other reported reactions (≥1%) include fatigue, fever, and headache (6.1, 6.2, 6.3)
To report SUSPECTED ADVERSE REACTIONS, contact Fougera at 1-800-645-9833 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: May 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Actinic Keratosis

Imiquimod Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.

1.2 Superficial Basal Cell Carcinoma

Imiquimod Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.

The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and efficacy of Imiquimod Cream have not been established for other types of basal cell carcinomas, including nodular and morpheaform (fibrosing or sclerosing) types.

1.3 External Genital Warts

Imiquimod Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older.

1.4 Limitations of Use

Imiquimod Cream has been evaluated in children ages 2 to 12 years with molluscum contagiosum and these studies failed to demonstrate efficacy. *[see Use in Specific Populations (8.4)*.

1.5 Unevaluated Populations

The safety and efficacy of Imiquimod Cream in immunosuppressed patients have not been established.

Imiquimod Cream should be used with caution in patients with pre-existing autoimmune conditions.

The efficacy and safety of Imiquimod Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

2 DOSAGE AND ADMINISTRATION

The application frequency for Imiquimod Cream is different for each indication.

Imiquimod is not for oral, ophthalmic, or intravaginal use.

2.1 Actinic Keratosis

Imiquimod Cream should be applied 2 times per week for a full 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area is defined as one contiguous area of approximately 25 cm^2 (e.g., 5 cm x 5 cm) on the face (e.g. forehead or one cheek) or on the scalp. Examples of 2 times per week application schedules are Monday and Thursday, or Tuesday and Friday. Imiquimod Cream should be applied to the entire treatment area and rubbed in until the cream is no longer visible. No more than one packet of Imiquimod Cream should be applied to the contiguous treatment area at each application. **Imiquimod Cream should be applied prior to normal sleeping hours and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.** The prescriber should demonstrate the proper application technique to maximize the benefit of Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly (at least 10 minutes).

Contact with the eyes, lips and nostrils should be avoided.

Local skin reactions in the treatment area are common. *[see Adverse Reactions (6.1, 6.5)]* A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. **However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.** Response to treatment cannot be adequately assessed until resolution of local skin reactions. Lesions that do not respond to treatment should be carefully re-evaluated and management reconsidered.

Imiquimod Cream is packaged in single-use packets, with 12 packets supplied per box.

Patients should be prescribed no more than 3 boxes (36 packets) for the 16-week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

2.2 Superficial Basal Cell Carcinoma

Imiquimod Cream should be applied 5 times per week for a full 6 weeks to a biopsy-confirmed superficial basal cell carcinoma. An example of a 5 times per week application schedule is to apply Imiquimod Cream, once per day, Monday through Friday. **Imiquimod Cream should be applied prior to normal sleeping hours and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.** The prescriber should demonstrate the proper application technique to maximize the benefit of Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream. The patient should wash the treatment area with mild soap and water before applying the cream, and allow the area to dry thoroughly.

The target tumor should have a maximum diameter of 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1 cm margin of skin around the tumor. Sufficient cream should be applied to cover the treatment area, including 1 centimeter of skin surrounding the tumor. Imiquimod Cream should be rubbed into the treatment area until the cream is no longer visible.

Table 1. Amount of Imiquimod Cream to use for sBBC

Target Tumor Diameter	Size of Cream Droplet to be Used (diameter)	Approximate Amount of Imiquimod Cream to be Used
0.5 to < 1.0 cm	4 mm	10 mg
≥ 1.0 to < 1.5 cm	5 mm	25 mg
≥ 1.5 to 2.0 cm	7 mm	40 mg

Contact with the eyes, lips and nostrils should be avoided.

Local skin reactions in the treatment area are common *[see Adverse Reactions (6.2, 6.5)]* A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. **Early clinical clearance cannot be adequately assessed until resolution of local skin reactions (e.g. 12 weeks post-treatment).** Local skin reactions or other findings (e.g. infection) may require that a patient be seen sooner than the post-treatment assessment for clinical clearance. If there is clinical evidence of persistent tumor at the post-treatment assessment for clinical clearance, a biopsy or other alternative intervention should be considered.

Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered, the safety and efficacy of a repeat course of Imiquimod Cream treatment have not been established. If any suspicious lesion arises in the treatment area at any time after a determination of clinical clearance, the patient should seek a medical evaluation. *[see Clinical Studies (14.2)]*.

Imiquimod Cream is packaged in single-use packets, with 12 packets supplied per box.

Patients should be prescribed no more than 3 boxes (36 packets) for the 6-week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

2.3 External Genital Warts

Imiquimod Cream should be applied 3 times per week to external genital/perianal warts. Imiquimod Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. **Imiquimod Cream should be applied prior to normal sleeping hours and left on the skin for 6 -10 hours, after which time the cream should be removed by washing the area with mild soap and water.** The prescriber should demonstrate the proper application technique to maximize the benefit of Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream.

A thin layer of Imiquimod Cream should not be applied to the wart area and rubbed in until the cream is no longer visible. The application site should not be occluded. Following the treatment period the cream should be removed by washing the treated area with mild soap and water. Local skin reactions at the treatment site are common. *[see Adverse Reactions (6.3, 6.5)]*. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions.

Imiquimod Cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided.

3 DOSAGE FORMS AND STRENGTHS

Imiquimod Cream 5%, is supplied in single-use packets each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. Imiquimod Cream is supplied in boxes of 12 packets each.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Inflammatory Reactions

Intense local inflammatory reactions including skin weeping or erosion can occur after few applications of Imiquimod Cream and may require an interruption of dosing. *[see Dosage and Administration (2) and Adverse Reactions (6)]*. Imiquimod Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Administration of Imiquimod Cream is not recommended until the skin is completely healed from any previous drug or surgical treatment.

5.2 Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered. *[see Adverse Reactions (6)]*.

5.3 Ultraviolet Light Exposure

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Imiquimod Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g., a hat) when using Imiquimod Cream. Patients with sunburn should be advised not to use Imiquimod Cream until fully recovered. Patients who may have considerable sun exposure, e.g. due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Imiquimod Cream.

Imiquimod Cream shortened the time to skin tumor formation in an animal photoco-carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

5.4 Unevaluated Uses: Actinic Keratosis

Safety and efficacy have not been established for Imiquimod Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same area.

The safety of Imiquimod Cream applied to areas of skin greater than 25 cm^2 (e.g. 5 cm X 5 cm) for the treatment of actinic keratosis has not been established *[see Clinical Pharmacology (12.3)]*.

5.5 Unevaluated Uses: Superficial Basal Cell Carcinoma

The safety and efficacy of Imiquimod Cream have not been established for other types of basal cell carcinomas (BCC), including nodular and morpheaform (fibrosing or sclerosing) types. **Imiquimod Cream is not recommended for treatment of BCC subtypes other than the superficial variant (i.e., sBCC).** Patients with sBCC treated with Imiquimod Cream should have regular follow-up of the treatment site. *[see Clinical Studies (14.2)]*.

The safety and efficacy of treating sBCC lesions on the face, head and anogenital area have not been established.

5.6 Unevaluated Uses: External Genital Warts

Imiquimod Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience: Actinic Keratosis

The data described below reflect exposure to Imiquimod Cream or vehicle in 436 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied Imiquimod Cream or vehicle to a 25 cm^2 contiguous treatment area on the face or scalp 2 times per week for 16 weeks.

Table 2: Selected Adverse Reactions Occurring in > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Preferred Term	Imiquimod Cream (n= 215)	Vehicle (n= 221)
Application Site Reaction	71 (33%)	32 (14%)
Upper Resp Tract Infection	33 (15%)	27 (12%)
Sinusitis	16 (7%)	14 (6%)
Headache	11 (5%)	7 (3%)
Carcinoma Squamous	8 (4%)	5 (2%)
Diarrhea	6 (3%)	2 (1%)
Eczema	4 (2%)	3 (1%)
Back Pain	3 (1%)	2 (1%)
Fatigue	3 (1%)	2 (1%)
Fibrillation Atrial	3 (1%)	2 (1%)
Infection Viral	3 (1%)	2 (1%)
Dizziness	3 (1%)	1 (<1%)
Vomiting	3 (1%)	1 (<1%)
Urinary Tract Infection	3 (1%)	1 (<1%)
Fever	3 (1%)	0 (0%)
Rigors	3 (1%)	0 (0%)
Alopecia	3 (1%)	0 (0%)

Table 3: Application Site Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Included Term	Imiquimod Cream n=215	Vehicle n=221
Itching	44 (20%)	17 (8%)
Burning	13 (6%)	4 (2%)
Bleeding	7 (3%)	1 (<1%)
Stinging	6 (3%)	2 (1%)
Pain	6 (3%)	2 (1%)
Induration	5 (2%)	3 (1%)
Tenderness	4 (2%)	3 (1%)
Irritation	4 (2%)	0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The most frequently reported local skin reactions were erythema, flaking/scaling/ dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 4: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Actinic Keratosis)

	Imiquimod Cream (n=215)		Vehicle (n=220)	
	All Grades*	Severe	All Grades*	Severe
Erythema	209 (97%)	38 (18%)	206 (93%)	5 (2%)
Flaking/Scaling/Dryness	199 (93%)	16 (7%)	199 (91%)	7 (3%)
Scabbing/Crusting	169 (79%)	18 (8%)	92 (42%)	4 (2%)
Edema	106 (49%)	0 (0%)	22 (10%)	0 (0%)
Erosion/Ulceration	103 (48%)	5 (2%)	20 (9%)	0 (0%)
Weeping/Exudate	45 (22%)	0 (0%)	3 (1%)	0 (0%)
Vesicles	19 (9%)	0 (0%)	2 (1%)	0 (0%)

*Mild, Moderate, or Severe

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies, 2% (5/215) of subjects discontinued for local skin/application site reactions. Of the 215 subjects treated, 35 subjects (16%) on Imiquimod Cream and 3 of 220 subjects (1%) on vehicle cream had at least one rest period. Of these Imiquimod Cream subjects, 32 (91%) resumed therapy after a rest period.

In the AK studies, 22 of 678 (3.2%) of Imiquimod-treated subjects developed treatment site infections that required a rest period off Imiquimod Cream and were treated with antibiotics (19 with oral and 3 with topical). Of the 206 Imiquimod subjects with both baseline and 8-week post-treatment scarring assessments, 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline.

6.2 Clinical Trials Experience: Superficial Basal Cell Carcinoma

The data described below reflect exposure to Imiquimod Cream or vehicle in 364 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied Imiquimod Cream or vehicle 5 times per week for 6 weeks. The incidence of adverse reactions reported by > 1% of subjects during the studies is summarized below.

Table 5: Selected Adverse Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Preferred Term	Imiquimod Cream (n= 185) N %	Vehicle (n= 179) N %
Application Site Reaction	52 (28%)	5 (3%)
Headache	14 (8%)	4 (2%)
Back Pain	7 (4%)	1 (<1%)
Upper Resp Tract Infection	6 (3%)	2 (1%)
Rhinitis	5 (3%)	1 (<1%)
Lymphadenopathy	5 (3%)	1 (<1%)
Fatigue	4 (2%)	2 (1%)
Sinusitis	4 (2%)	1 (<1%)
Dyspepsia	3 (2%)	2 (1%)
Coughing	3 (2%)	1 (<1%)
Fever	3 (2%)	0 (0%)
Dizziness	2 (1%)	1 (<1%)
Anxiety	2 (1%)	1 (<1%)
Pharyngitis	2 (1%)	1 (<1%)
Chest Pain	2 (1%)	0 (0%)
Nausea	2 (1%)	0 (0%)

The most frequently reported adverse reactions were local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The incidence of application site reactions reported by > 1% of the subjects during the 6 week treatment period is summarized in the table below.

Table 6: Application Site Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Included Term	Imiquimod Cream n=185	Vehicle n=179
Itching	30 (16%)	1 (1%)
Burning	11 (6%)	2 (1%)
Pain	6 (3%)	0 (0%)
Bleeding	4 (2%)	0 (0%)
Erythema	3 (2%)	0 (0%)
Papule(s)	3 (2%)	0 (0%)
Tenderness	2 (1%)	0 (0%)
Infection	2 (1%)	0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 7: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Superficial Basal Cell Carcinoma)

	Imiquimod Cream n=184		Vehicle n=178	
	All Grades*	Severe	All Grades*	Severe
Erythema	184 (100%)	57 (31%)	173 (97%)	4 (2%)
Flaking/Scaling	167 (91%)	7 (4%)	135 (76%)	0 (0%)
Induration	154 (84%)	11 (6%)	94 (53%)	0 (0%)
Scabbing/Crusting	152 (83%)	35 (19%)	61 (34%)	0 (0%)
Edema	143 (78%)	13 (7%)	64 (36%)	0 (0%)
Erosion	122 (66%)	23 (13%)	25 (14%)	0 (0%)
Ulceration	73 (40%)	11 (6%)	6 (3%)	0 (0%)
Vesicles	57 (31%)	3 (2%)	4 (2%)	0 (0%)

*Mild, Moderate, or Severe

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions; 10% (19/185) of subjects received rest periods.

The average number of doses not received per subject due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of subjects (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of subjects discontinued for local skin/application site reactions. In the sBCC studies, 17 of 1266 (1.3%) Imiquimod -treated subjects developed treatment site infections that required a rest period and treatment with antibiotics.

6.3 Clinical Trials Experience: External Genital Warts

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Table 8: Local Skin Reactions in theTreatment Area as Assessed by the Investigator (External Genital Warts)

	Imiquimod Cream				Vehicle			
	Females n=114		Males n=156		Females n=99		Males n=157	
	All Grades*	Severe	All Grades*	Severe	All Grades*	Severe	All Grades*	Severe
Erythema	74(65%)	4(4%)	90(58%)	6(4%)	21(21%)	0(0%)	34(22%)	0(0%)
Erosion	5(31%)	1(1%)	47(30%)	2(1%)	8(8%)	0(0%)	10(6%)	0(0%)
Excoriation/ Flaking	21(18%)	0(0%)	40(26%)	1(1%)	8(8%)	0(0%)	12(8%)	0(0%)
Edema	20(18%)	1(1%)	19(12%)	0(0%)	5(5%)	0(0%)	1(1%)	0(0%)
Scabbing	4(4%)	0(0%)	20(13%)	0(0%)	0(0%)	0(0%)	4(3%)	0(0%)
Induration	6(5%)	0(0%)	11(7%)	0(0%)	2(2%)	0(0%)	3(2%)	0(0%)
Ulceration	9(8%)	3(3%)	7(4%)	0(0%)	1(1%)	0(0%)	1(1%)	0(0%)
Vesicles	3(3%)	0(0%)	3(2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

Selected adverse reactions judged to be probably or possibly related to Imiquimod Cream are listed below.

Table 9: Selected Treatment Related Reactions (External Genital Warts)

	Females		Males	
	Imiquimod Cream n=117	Vehicle n=103	ImiquimodCream n=156	Vehicle n=158
Application Site Disorders: Application Site Reactions **Wart Site:**				
Itching	38(32%)	21(20%)	34(22%)	16(10%)
Burning	30(26%)	12(12%)	14(9%)	8(5%)
Pain	9(8%)	2(2%)	3(2%)	1(1%)
Soreness	3(3%)	0(0%)	0(0%)	1(1%)
Fungal Infection*	13(11%)	3(3%)	3(2%)	1(1%)
Systemic Reactions:				
Headache	5(4%)	3(3%)	8(5%)	3(2%)
Influenza-like symptoms	4(3%)	2(2%)	2(1%)	0(0%)
Myalgia	1(1%)	0(0%)	2(1%)	1(1%)

*Incidences reported without regard to causality with Imiquimod Cream.

Adverse reactions judged to be possibly or probably related to Imiquimod Cream and reported by more than 1% of subjects included:
Application Site Disorders: burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness
Remote Site Reactions: bleeding, burning, itching, pain, tenderness, tinea cruris
Body as a Whole: fatigue, fever, influenza-like symptoms
Central and Peripheral Nervous System Disorders: headache
Gastro-Intestinal System Disorders: diarrhea
Musculo-Skeletal System Disorders: myalgia.

6.4 Clinical Trials Experience: Dermal Safety Studies

Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that Imiquimod Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Imiquimod Cream to cause irritation, and application site reactions were reported in the clinical studies *[see Adverse Reactions (6)]*.

6.5 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Imiquimod Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Body as a Whole: angioedema.
Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope.
Endocrine: thyroiditis.
Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma
Hepatic: abnormal liver function
Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide.
Respiratory: dyspnea.
Urinary System Disorders: proteinuria.
Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation.
Vascular: Henoch-Schonlein purpura syndrome

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C:

Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Imiquimod Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of Imiquimod Cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of Imiquimod Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects *[see Clinical Pharmacology (12.3)]*. The AUC after topical application of 6 packets of Imiquimod Cream was 8 fold greater than the AUC after topical application of 2 packets of Imiquimod Cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of Imiquimod Cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/6 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label.

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 (577X 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 (90X 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 (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (87X 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 (87X 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 (87X 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 (41X MRHD based on AUC comparisons).

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

8.3 Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of Imiquimod Cream. Because many drugs are excreted in human milk, caution should be exercised when Imiquimod Cream is administered to nursing women.

8.4 Pediatric Use

AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Imiquimod Cream for AK or sBCC in patients less than 18 years of age have not been established.

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

Imiquimod Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Imiquimod; median age 5 years, range 2-12 years). Subjects applied Imiquimod Cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC lesions) was assessed at Week 18. In Study 1, the complete clearance rate was 24% (52/217) in the Imiquimod Cream group compared with 28% (28/106) in the vehicle group. In Study 2, the clearance rates were 24% (60/253) in the Imiquimod Cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy.

Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with molluscum contagiosum was application site reaction. Adverse events which occurred more frequently in Imiquimod-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Imiquimod vs. 3% vehicle) and conjunctivitis (3% Imiquimod vs. 2% vehicle).

Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Imiquimod-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%).

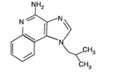
Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject's weight. The overall median peak serum drug concentrations at the end of week 4 were between 0.26 and 1.06 ng/ml except in a 2-year old female who was administered 2 packets of study drug per dose, had a Cmax of 9.66 ng/mL after multiple dosing. Children aged 2-5 years received doses of 12.5 mg (one packet) or 25 mg (two packets) of imiquimod and had median multiple-dose peak serum drug levels of approximately 0.2 or 0.5 ng/mL, respectively.

Children aged 6-12 years received doses of 12.5 mg, 25 mg, or 37.5 mg (three packets) and had median multiple dose serum drug levels of approximately 0.1, 0.15, or 0.3 ng/mL, respectively. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/L.

8.5 Geriatric Use
Of the 215 subjects treated with Imiquimod Cream in the AK clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Imiquimod Cream in the sBCC clinical studies , 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE
Topical overdosing of Imiquimod Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.
The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

11 DESCRIPTION
Imiquimod Cream 5% is an immune response modifier for topical administration. Each gram contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of oleic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.
Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of Imiquimod Cream in treating AK and sBCC lesions is unknown.
12.2 Pharmacodynamics
Actinic Keratosis
In a study of 18 subjects with AK comparing Imiquimod Cream to vehicle, increases from baseline in week 2 biomarker levels were reported for CD3, CD4, CD8, CD11c, and CD68 for Imiquimod Cream treated subjects; however, the clinical relevance of these findings is unknown.
Superficial Basal Cell Carcinoma
An open label study in six subjects with sBCC suggests that treatment with Imiquimod Cream may increase the infiltration of lymphocytes, dendritic cells, and macrophages into the tumor lesion; however, the clinical significance of these findings is unknown.
External Genital Warts
Imiquimod has no direct antiviral activity in cell culture. A study in 22 subjects with genital/perianal warts comparing Imiquimod Cream and vehicle shows that Imiquimod Cream induces mRNA encoding cytokines including interferon-α at the treatment site. In addition HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

12.3 Pharmacokinetics
Systemic absorption of imiquimod across the affected skin of 58 subjects with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean peak serum drug concentrations at the end of week 16 were approximately 0.1, 0.2, and 3.5 ng/mL for the applications to face (12.5 mg imiquimod, 1 single-use packet), scalp (25 mg, 2 packets) and hands/arms (75 mg, 6 packets), respectively.

Table 10: Mean Serum Imiquimod Concentration in Adults Following Administration of the Last Topical Dose During Week 16 (Actinic Keratosis)

Amount of Imiquimod Cream applied	Mean peak serum imiquimod concentration [Cmax]
12.5 mg (1 packet)	0.1 ng/mL
25 mg (2 packets)	0.2 ng/mL
75 mg (6 packets)	3.5 ng/mL

The application surface area was not controlled when more than one packet was used. Dose proportionality was not observed. However it appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life was approximately 10 times greater with topical dosing than the 2 hour apparent half-life seen following subcutaneous dosing, suggesting prolonged retention of drug in the skin. Mean urinary recoveries of imiquimod and metabolites combined were 0.08 and 0.15% of the applied dose in the group using 75 mg (6 packets) for males and females, respectively following 3 applications per week for 16 weeks.
Systemic absorption of imiquimod was observed across the affected skin of 12 subjects with genital/perianal warts, with an average dose of 4.6 mg. Mean peak drug concentration of approximately 0.4 ng/mL was seen during the study. Mean urinary recoveries of imiquimod and metabolites combined over the whole course of treatment, expressed as percent of the estimated applied dose, were 0.11 and 2.41% in the males and females, respectively.

13 NONCLINICAL TOXICOLOGY
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 (67X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X 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 (251X 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 Imiquimod 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 (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Imiquimod 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.
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 67X MRHD based on AUC comparisons.

14 CLINICAL STUDIES
14.1 Actinic Keratosis
In two double-blind, vehicle-controlled clinical studies, 436 subjects with AK were randomized to treatment with either Imiquimod Cream or vehicle cream 2 times per week for 16 weeks. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on either the face or scalp. The 25 cm^2 contiguous treatment area could be of any dimensions e.g., 5 cm x 5 cm, 3 cm by 8.3 cm, 2 cm by 12.5 cm. Study subjects ranged from 37 to 88 years of age (median 66 years) and 59% had Fitzpatrick skin type I or II. All imiquimod-treated subjects were Caucasians.
On a scheduled dosing day, the study cream was applied to the entire treatment area prior to normal sleeping hours and left on for approximately 8 hours. Twice weekly dosing was continued for a total of 16 weeks. The clinical response of each subject was evaluated 8 weeks after the last scheduled application of study cream. Efficacy was assessed by the complete clearance rate, defined as the proportion of subjects at the 8-week post-treatment visit with no (zero) clinically visible AK lesions in the treatment area. Complete clearance included clearance of all baseline lesions, as well as any new or sub-clinical AK lesions which appeared during therapy.
Complete and partial clearance rates are shown in the table below. The partial clearance rate was defined as the percentage of subjects in whom 75% or more baseline AK lesions were cleared.

Table 11: Clearance Rates (AK)
Complete Clearance Rates (100% AK Lesions Cleared)

Study	Imiquimod Cream	Vehicle
Study AK1	46% (49/107)	3% (3/110)
Study AK2	44% (48/108)	4% (4/111)

Partial and Complete Clearance Rates (75% or More Baseline AK Lesions Cleared)

Study	Imiquimod Cream	Vehicle
Study AK1	60% (64/107)	10% (11/110)
Study AK2	58% (63/108)	14% (15/111)

Sub-clinical AK lesions may become apparent in the treatment area during treatment with Imiquimod Cream. During the course of treatment, 46% (103/215) of subjects experienced an increase in AK lesions relative to the number present at baseline within the treatment area. Subjects with an increase in AK lesions had a similar response to those with no increase in AK lesions.

14.2 Superficial Basal Cell Carcinoma
In two double-blind, vehicle-controlled clinical studies, 364 subjects with primary sBCC were treated with Imiquimod Cream or vehicle cream5 times per week for 6 weeks. Target tumors were biopsy-confirmed sBCC and had a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm (4.0 cm^2). Target tumors were not to be located within 1.0 cm of the hairline, or on the anogenital area or on the hands or feet, or to have any atypical features. The population ranged from 31-89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. On a scheduled dosing day, study cream was applied to the target tumor and approximately 1 cm (about 1/3 inch) beyond the target tumor prior to normal sleeping hours, and 5 times per week dosing was continued for a total of 6 weeks. The target tumor area was clinically assessed 12 weeks after the last scheduled application of study cream. The entire target tumor was then excised and examined histologically for the presence of tumor.
Efficacy was assessed by the complete response rate defined as the proportion of subjects with clinical (visual) and histological clearance of the sBCC lesion at 12 weeks post-treatment. Of Imiquimod-treated subjects, 6% (11/178) who had both clinical and histological assessments posttreatment, and who appeared to be clinically clear had evidence of tumor on excision of the clinically-clear treatment area.
Data on composite clearance (defined as both clinical and histological clearance) are shown in the table below.

Table 12: Composite Clearance Rates at 12 Weeks Post-Treatment for Superficial Basal Cell Carcinoma

Study	Imiquimod Cream	Vehicle Cream
Study sBCC1	70% (66/94)	2% (2/89)
Study sBCC2	80% (73/91)	1% (1/90)
Total	75% (139/185)	2% (3/179)

A separate 5-year, open-label study is ongoing to assess the recurrence of sBCC treated with Imiquimod Cream applied once daily 5 days per week for 6 weeks. Target tumor inclusion criteria were the same as for the studies described above. At 12-weeks post-treatment, subjects were clinically evaluated for evidence of persistent sBCC (no histological assessment). Subjects with no clinical evidence of sBCC entered the long-term follow-up period. At the 12 week posttreatment assessment, 90% (163/182) of the subjects enrolled had no clinical evidence of sBCC at their target site and 162 subjects entered the long-term follow-up period for up to 5 years. Two year (24 month) follow-up data are available from this study and are presented in the table below:

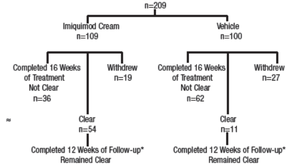
Table 13: Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma

	Follow-up Period			
Follow-up visit after 12-week post-treatment assessment	No. of Subjects who remained clinically clear	No. of Subjects with sBCC recurrance	No. of Subjects who discontinued at this visit with no sBCC[b]	Estimated rate of Subjects who Clinically Cleared and remained Cleared[b]
Month 3	153	4	5	87%
Month 6	149	4	0	85%
Month 12	143	2	4	84%
Month 24	139	4	0	79%

a Reasons for discontinuation included death, non-compliance, entry criteria violations, personal reasons, and treatment of nearby sBCC tumor.
b Estimated rate of subjects who clinically cleared and remained clear are estimated based on the time to event analysis employing the life table method beginning with the rate of clinical clearance at 12 weeks post-treatment.

14.3 External Genital Warts
In a double-blind, placebo-controlled clinical study, 209 otherwise healthy subjects 18 years of age and older with genital/perianal warts were treated with Imiquimod Cream or vehicle control times per week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2).
Subject accountability is shown in the figure below.

Figure 1: Subject Accountability (External Genital Warts)



*The other subjects were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Table 14: Complete Clearance Rates (External Genital Warts)- Study EGW1

Treatment	Subjects with Complete Clearance of Warts	Subjects Without Follow-up	Subjects with Warts Remaining at Week 16
Overall			
Imiquimod Cream (n =109)	54 (50%)	19 (17%)	36 (33%)
Vehicle (n =100)	11 (11%)	27 (27%)	62 (62%)
Females			
Imiquimod Cream (n =46)	33 (72%)	5 (11%)	8 (17%)
Vehicle (n =40)	8 (20%)	13 (33%)	19 (48%)
Males			
Imiquimod Cream (n =63)	21 (33%)	14 (22%)	28 (44%)
Vehicle (n =60)	3 (5%)	14 (23%)	43 (72%)

16 HOW SUPPLIED/STORAGE AND HANDLING
Imiquimod Cream, 5%, is supplied in single-use packets which contain 250 mg of the cream.
Available as: box of 12 packets NDC 0168-0432-26. Store at 4 - 25°C (39 - 77°F) Avoid freezing.
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (17.7)

17.1 General Information: All Indications
Imiquimod Cream should be used as directed by a physician. *[see Dosage and Administration (2)]*
Imiquimod Cream is for external use only. Contact with the eyes, lips and nostrils should be avoided. *[see Indications and Usage (1) and Dosage and Administration (2)]* The treatment area should not be bandaged or otherwise occluded. Partially-used packets should be discarded and not reused. The prescriber should demonstrate the proper application technique to maximize the benefit of Imiquimod Cream therapy.
It is recommended that patients wash their hands before and after applying Imiquimod cream.

17.2 Local Skin Reactions: All Indications
Patients may experience local skin reactions during treatment with Imiquimod Cream (even with normal dosing). Potential local skin reactions include erythema, edema, vesicles, erosions/ulcerations, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. These reactions can range from mild to severe in intensity and may extend beyond the application site onto the surrounding skin. Patients may also experience application site reactions such as itching and/or burning. *[see Adverse Reactions (6)]*

Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Imiquimod Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult. Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. Localized hypopigmentation and hyperpigmentation have been reported following use of Imiquimod Cream. These skin color changes may be permanent in some patients.

17.3 Systemic Reactions: All Indications
Patients may experience flu-like systemic signs and symptoms during treatment with Imiquimod Cream (even with normal dosing). Systemic signs and symptoms may include malaise, fever, nausea, myalgias and rigors. *[see Adverse Reactions (6)]* An interruption of dosing should be considered.

17. 4 Patients Being Treated for Actinic Keratosis (AK)
Dosing is 2 times per week for a full 16 weeks, unless otherwise directed by the physician.
However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods. *[see Dosage and Administration (2.1)]*

It is recommended that the treatment area be washed with mild soap and water 8 hours following Imiquimod Cream application.

Most patients using Imiquimod Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. *[see Adverse Reactions (6.1)]*

Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Imiquimod Cream. *[see Warnings and Precautions (5.3)]*

Sub-clinical AK lesions may become apparent in the treatment area during treatment and may subsequently resolve. *[see Clinical Studies (16.1)]*

17.5 Patients Being Treated for Superficial Basal Cell Carcinoma (sBCC)
Dosing is 5 times per week for a full 6 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 6 weeks due to missed doses or rest periods. *[see Dosage and Administration (2.2)]*

It is recommended that the treatment area be washed with mild soap and water 8 hours following Imiquimod Cream application. *[see Dosage and Administration (2.2)]*

Most patients using Imiquimod Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. *[see Adverse Reactions (6.2)]*

Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Imiquimod Cream. *[see Warnings and Precautions (5.7)]*

The clinical outcome of therapy can be determined after resolution of application site reactions and/or local skin reactions.

Patients with sBCC treated with Imiquimod Cream should have regular follow-up to re-evaluate the treatment site. *[see Clinical Studies (16.2)]*

17.6 Patients Being Treated for External Genital Warts
Dosing is 3 times per week to external genital/perianal warts. Imiquimod Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks.

It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Imiquimod Cream application.

It is common for patients to experience local skin reactions such as erythema, erosion,excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate.

Sexual (genital, anal, oral) contact should be avoided while Imiquimod Cream is on the skin.
Application of Imiquimod Cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.

Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

New warts may develop during therapy, as Imiquimod Cream is not a cure.

The effect of Imiquimod Cream on the transmission of genital/perianal warts is unknown.

Imiquimod Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.

Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water.

17.7 FDA-Approved Patient Labeling

E. FOUGERA & CO
A division of Nycomed US Inc.
Melville, New York 11747

IF2432
R1/08

Patient Information
IMIQUIMOD Cream, 5%
IMPORTANT: Not for mouth, eye, or vaginal use

Read the Patient Information that comes with Imiquimod Cream before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment. If you do not understand the information, or have any questions about Imiquimod Cream, talk with your healthcare provider or pharmacist.
What is Imiquimod Cream?
Imiquimod Cream is a skin use only (topical) medicine used to treat:
- external genital and perianal warts in people 12 years and older
- actinic keratosis in adults with normal immune systems. Actinic keratosis is caused by too much sun exposure.
- superficial basal cell carcinoma in adults with normal immune systems when surgical methods are less appropriate. This skin cancer needs to be diagnosed by your healthcare provider.

Imiquimod Cream is used in different ways for the three different skin conditions it is used to treat. It is very important that you follow the instructions for your skin condition. Talk to your healthcare provider if you have questions.

Imiquimod Cream does not work for everyone. Imiquimod Cream will not cure your genital or perianal warts. New warts may develop during treatment with Imiquimod Cream. It is not known if Imiquimod Cream can stop you from spreading genital or perianal warts to other people. For your own health and the health of others, it is important to practice safer sex.Talk to your healthcare provider about safer sex practices.

Who should not use Imiquimod Cream?
- Imiquimod Cream has not been studied in children under 12 years old for external genital and perianal warts.
- Imiquimod Cream has not been studied in children under 18 years old for actinic keratosis or superficial basal cell carcinoma. Children usually do not get actinic keratoses or basal cell carcinoma.

Before using Imiquimod Cream, tell your healthcare provider:
- about all your medical conditions, including if you
  - are pregnant or planning to become pregnant. It is not known if Imiquimod Cream can harm your unborn baby.
  - are breastfeeding. It is not known if Imiquimod Cream passes into your milk and if it can harm your baby.
- about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you have had other treatments for genital or perianal warts, or actinic keratosis, or superficial basal cell carcinoma.
  Imiquimod Cream should not be used until your skin has healed from other treatments.

How should I use Imiquimod Cream?
- Use Imiquimod Cream exactly as prescribed by your healthcare provider. **Imiquimod Cream is for skin use only. Do not take by mouth or use in or near your eyes, lips or nostrils.**
  Do not use Imiquimod Cream unless your healthcare provider has taught you the right way to use it. Talk to your healthcare provider if you have any questions.
- Imiquimod Cream is used for several skin conditions. **Use Imiquimod cream only on the area of your body to be treated.** Your healthcare provider will tell you where to apply Imiquimod Cream and how often and for how long to apply it for your condition. Do not use Imiquimod Cream longer than prescribed. Using too much Imiquimod Cream, or using it too often, or for too long can increase your chances for having a severe skin reaction or other side effect. Talk to your healthcare provider if Imiquimod Cream does not work for you.

For external genital and perianal warts Imiquimod Cream is usually used once a day for 3 days a week:
- Monday, Wednesday and Friday, or
- Tuesday, Thursday and Saturday

For these conditions, Imiquimod Cream is usually left on the skin for 6 to 10 hours. Treatment should continue until the warts are completely gone, or up to 16 weeks.

For actinic keratosis Imiquimod Cream is usually used once a day for 2 days a week, 3 to 4 days apart, such as:
- Monday and Thursday, or
- Tuesday and Friday

For this condition, Imiquimod Cream is usually left on the skin for about 8 hours. Treatment should continue for the full 16 weeks even if all actinic keratoses appear to be gone, unless you are told otherwise by your healthcare provider. The area you treat with Imiquimod Cream should be no larger than approximately the size of your forehead or one cheek (for example 2 inches by 2 inches), unless otherwise directed by your healthcare provider.

For superficial basal cell carcinoma Imiquimod Cream is usually used once a day for 5 days a week:
- Monday, Tuesday, Wednesday, Thursday and Friday

For this condition, Imiquimod Cream is usually left on the skin for about 8 hours. Your healthcare provider will show you how much Imiquimod Cream to apply to your superficial basal cell carcinoma. You should also apply Imiquimod Cream to a small area of skin all around the superficial basal cell carcinoma. This small area of skin should be about the size of your fingertip. Treatment should continue for the full 6 weeks, even if the superficial basal cell carcinoma appears to be gone, unless you are told otherwise by your healthcare provider.

Applying Imiquimod Cream
Imiquimod Cream should be applied just before your bedtime.
- Wash the area to be treated with mild soap and water. Allow the area to dry.
  - Uncircumcised males treating warts under their penis foreskin must pull their foreskin back and clean before treatment, and clean daily during the weeks of treatment.
- Wash your hands
- Open a new packet of Imiquimod Cream just before use
- Apply a thin layer of Imiquimod Cream **only** to the affected area or areas to be treated.
  Do not use more Imiquimod cream than is needed to cover the treatment area.
- Rub the cream in all the way to the affected area or areas.
  - Do not get Imiquimod Cream in your eyes.
  - Do not get Imiquimod Cream in the anus when applying to perianal warts.
  - Female patients treating genital warts must be careful when applying Imiquimod Cream around the vaginal opening. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can cause pain or swelling, and may cause problems passing urine. Do not put Imiquimod Cream in your vagina or on the skin around the genital wart.
- Do not cover the treated area with an airtight bandage. Cotton gauze dressings can be used. Cotton underwear can be worn after applying Imiquimod Cream to the genital or perianal area.
- Safely throw away the open packet of Imiquimod Cream so that children and pets cannot get it. The open packet should be thrown away even if all the Imiquimod Cream was not completely used.
- After applying Imiquimod Cream, **wash your hands well.**
- Leave the cream on the affected area or areas for the time prescribed by your healthcare provider. The length of time that Imiquimod Cream is left on the skin is not the same for the different skin conditions that Imiquimod Cream is used to treat. Do not bathe or get the treated area wet before the right time has passed. Do not leave Imiquimod Cream on your skin longer than prescribed.
- After the right amount of time has passed, wash the treated area or areas with mild soap and water.
- If you forget to apply Imiquimod Cream, apply the missed dose of cream as soon as you remember and then continue on your regular schedule.
- If you get Imiquimod Cream in your mouth or in your eyes rinse well with water right away.

What should I avoid while using Imiquimod Cream?
- Do not cover the treated site with bandages or other closed dressings. Cotton gauze dressings are okay to use, if needed. Cotton underwear can be worn after treating the genital or perianal area.
- Do not apply Imiquimod Cream in or near the eyes, lips or nostrils, or in the vagina or anus.
- Do not use sunlamps or tanning beds, and avoid sunlight as much as possible during treatment with Imiquimod Cream. Use sunscreen and wear protective clothing if you go outside during daylight.
- Do not have sexual contact including genital, anal, or oral sex when Imiquimod Cream is on your genital or perianal skin. Imiquimod Cream may weaken condoms and vaginal diaphragms. This means they may not work as well to prevent pregnancy. For your own health and the health of others, it is important to practice safer sex. Talk to your healthcare provider about safer sex practices.

What are the possible side effects of Imiquimod Cream?
The most common side effects with Imiquimod Cream are skin reactions at the treatment site including:
- redness
- swelling
- a sore, blister, or ulcer
- skin that becomes hard or thickened
- skin peeling
- scabbing and crusting
- itching
- burning
- changes in skin color that do not always go away

Actinic Keratosis
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, scabbing, itching and burning are common at the site where Imiquimod Cream is applied, and sometimes the side effects go outside of the area where Imiquimod Cream was applied. Swelling, small open sores and drainage may also be experienced with use of Imiquimod Cream. You may also experience itching and/or burning. Actinic keratoses that were not seen before may appear during treatment and may later go away. If you have questions regarding treatment or skin reactions, please talk with your healthcare provider.

Superficial Basal Cell Carcinoma
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, swelling and a sore are common at the site where Imiquimod Cream is applied. You may also experience itching or burning. Your healthcare provider will need to check the area that was treated after your treatment is finished to make sure that the skin cancer is gone. Superficial basal cell carcinoma can come back. The chances of it coming back are higher as time passes. **It is very important to have regular follow-up visits with your healthcare provider to check the area to make sure your skin cancer has not come back. Ask your healthcare provider how often you should have your skin checked.** Talk with your healthcare provider if you have questions about your treatment or skin reactions.

External Genital and Perianal Warts
Patients should be aware that new warts may develop during treatment, as Imiquimod Cream is not a cure. Many people see reddening or swelling on or around the application site during the course of treatment. If you have questions regarding treatment or local skin reactions, please talk with your healthcare provider. You have a higher chance for severe skin reactions if you use too much Imiquimod Cream or use it the wrong way. Stop Imiquimod Cream **right away and call your healthcare provider if you get any skin reactions that affect your daily activities, or that do not go away.** Sometimes, Imiquimod Cream must be stopped for a while to allow your skin to heal. Talk to your healthcare provider if you have questions about your treatment or skin reactions. Other side effects of Imiquimod Cream include headache, back pain, muscle aches, tiredness, flu-like symptoms, swollen lymph nodes, diarrhea, and fungal infections.
If the reactions seem excessive, if either skin breaks down or sores develop during the first week of treatment, if flu-like symptoms develop or if you begin to not feel well at anytime, contact your healthcare provider.

These are not all the side effects of Imiquimod Cream. For more information, ask your healthcare provider or pharmacist.

How do I store Imiquimod Cream?
- Store Imiquimod Cream at 39 - 77° F (4 - 25° C). Do not freeze.
- Safely throw away Imiquimod Cream that is out of date or that you do not need.
- **Keep Imiquimod Cream and all medicines out of the reach of children.**

General information about Imiquimod Cream
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Imiquimod Cream for a condition for which it was not prescribed. Do not give Imiquimod Cream to other people, even if they have the same symptoms you have. This leaflet summarizes the most important information about Imiquimod Cream. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Imiquimod Cream that is written for the healthcare provider.
If you have other questions about Imiquimod Cream, call 1-800-645-9833
What are the ingredients in Imiquimod Cream?
Active Ingredient: imiquimod
Inactive Ingredients: oleic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

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℞ only

Patient Information
IMIQUIMOD Cream, 5%

IMPORTANT: Not for mouth, eye, or vaginal use

Read the Patient Information that comes with Imiquimod Cream before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment. If you do not understand the information, or have any questions about Imiquimod Cream, talk with your healthcare provider or pharmacist.

What is Imiquimod Cream?
Imiquimod Cream is a skin use only (topical) medicine used to treat:
- external genital and perianal warts in people 12 years and older
- actinic keratosis in adults with normal immune systems. Actinic keratosis is caused by too much sun exposure.
- superficial basal cell carcinoma in adults with normal immune systems when surgical methods are less appropriate. This skin cancer needs to be diagnosed by your healthcare provider.

Imiquimod Cream is used in different ways for the three different skin conditions it is used to treat. It is very important that you follow the instructions for your skin condition. Talk to your healthcare provider if you have questions.

Imiquimod Cream does not work for everyone. Imiquimod Cream will not cure your genital or perianal warts. New warts may develop during treatment with Imiquimod Cream. It is not known if Imiquimod Cream can stop you from spreading genital or perianal warts to other people. For your own health and the health of others, it is important to practice safer sex. Talk to your healthcare provider about safer sex practices.

Who should not use Imiquimod Cream?
- Imiquimod Cream has not been studied in children under 12 years old for external genital and perianal warts.
- Imiquimod Cream has not been studied in children under 18 years old for actinic keratosis or superficial basal cell carcinoma. Children usually do not get actinic keratoses or basal cell carcinoma.

Before using Imiquimod Cream, tell your healthcare provider:
- **about all your medical conditions, including if you**
  - o **are pregnant or planning to become pregnant.** It is not known if Imiquimod Cream can harm your unborn baby.
  - o **are breastfeeding.** It is not known if Imiquimod Cream passes into your milk and if it can harm your baby.
- **about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements.** Especially tell your healthcare provider if you have had other treatments for genital or perianal warts, or actinic keratosis, or superficial basal cell carcinoma. Imiquimod Cream should not be used until your skin has healed from other treatments.

How should I use Imiquimod Cream?
- Use Imiquimod Cream exactly as prescribed by your healthcare provider. **Imiquimod Cream is for skin use only. Do not take by mouth or use in or near your eyes, lips or nostrils.** Do not use Imiquimod Cream unless your healthcare provider has taught you the right way to use it. Talk to your healthcare provider if you have any questions.
- Imiquimod Cream is used for several skin conditions. **Use Imiquimod Cream only on the area of your body to be treated.** Your healthcare provider will tell you where to apply Imiquimod Cream and how often and for how long to apply it for your condition. Do not use Imiquimod Cream longer than prescribed. Using too much Imiquimod Cream, or using it too often, or for too long can increase your chances for having a severe skin reaction or other side effect. Talk to your healthcare provider if Imiquimod Cream does not work for you.

For external genital and perianal warts Imiquimod Cream is usually used once a day for 3 days a week:
- Monday, Wednesday and Friday, or
- Tuesday, Thursday and Saturday

For these conditions, Imiquimod Cream is usually left on the skin for 6 to 10 hours. Treatment should continue until the warts are completely gone, or up to 16 weeks.

For actinic keratosis Imiquimod Cream is usually used once a day for 2 days a week, 3 to 4 days apart, such as:
- Monday and Thursday, or
- Tuesday and Friday

For this condition, Imiquimod Cream is usually left on the skin for about 8 hours. Treatment should continue for the full 16 weeks even if all actinic keratoses appear to be gone, unless you are told otherwise by your healthcare provider. The area you treat with Imiquimod Cream should be no larger than approximately the size of your forehead or one cheek (for example 2 inches by 2 inches), unless otherwise directed by your healthcare provider.

For superficial basal cell carcinoma Imiquimod Cream is usually used once a day for 5 days a week:
- Monday, Tuesday, Wednesday, Thursday and Friday

For this condition, Imiquimod Cream is usually left on the skin for about 8 hours. Your healthcare provider will show you how much Imiquimod Cream to apply to your superficial basal cell carcinoma. You should also apply Imiquimod Cream to a small area of skin all around the superficial basal cell carcinoma. This small area of skin should be about the size of your fingertip. Treatment should continue for the full 6 weeks, even if the superficial basal cell carcinoma appears to be gone, unless you are told otherwise by your healthcare provider.

Applying Imiquimod Cream
Imiquimod Cream should be applied just before your bedtime.
- Wash the area to be treated with mild soap and water. Allow the area to dry.
  - o Uncircumcised males treating warts under their penis foreskin must pull their foreskin back and clean before treatment, and clean daily during the weeks of treatment.
- Wash your hands
- Open a new packet of Imiquimod Cream just before use
- Apply a thin layer of Imiquimod Cream **only** to the affected area or areas to be treated. Do not use more Imiquimod cream than is needed to cover the treatment area.
- Rub the cream in all the way to the affected area or areas.
  - o Do not get Imiquimod Cream in your eyes.
  - o Do not get Imiquimod Cream in the anus when applying to perianal warts.
  - o Female patients treating genital warts must be careful when applying Imiquimod Cream around the vaginal opening. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can cause pain or swelling, and may cause problems passing urine. Do not put Imiquimod Cream in your vagina or on the skin around the genital wart.
- Do not cover the treated area with an airtight bandage. Cotton gauze dressings can be used. Cotton underwear can be worn after applying Imiquimod Cream to the genital or perianal area.

• Safely throw away the open packet of Imiquimod Cream so that children and pets cannot get it. The open packet should be thrown away even if all the Imiquimod Cream was not completely used.
• After applying Imiquimod Cream, **wash your hands well.**
• Leave the cream on the affected area or areas for the time prescribed by your healthcare provider. The length of time that Imiquimod Cream is left on the skin is not the same for the different skin conditions that Imiquimod Cream is used to treat. Do not bathe or get the treated area wet before the right time has passed. Do not leave Imiquimod Cream on your skin longer than prescribed.
• After the right amount of time has passed, wash the treated area or areas with mild soap and water.
• If you forget to apply Imiquimod Cream, apply the missed dose of cream as soon as you remember and then continue on your regular schedule.
• If you get Imiquimod Cream in your mouth or in your eyes rinse well with water right away.

What should I avoid while using Imiquimod Cream?
• Do not cover the treated site with bandages or other closed dressings. Cotton gauze dressings are okay to use, if needed. Cotton underwear can be worn after treating the genital or perianal area.
• Do not apply Imiquimod Cream in or near the eyes, lips or nostrils, or in the vagina or anus.
• Do not use sunlamps or tanning beds, and avoid sunlight as much as possible during treatment with Imiquimod Cream. Use sunscreen and wear protective clothing if you go outside during daylight.
• Do not have sexual contact including genital, anal, or oral sex when Imiquimod Cream is on your genital or perianal skin. Imiquimod Cream may weaken condoms and vaginal diaphragms. This means they may not work as well to prevent pregnancy. For your own health and the health of others, it is important to practice safer sex. Talk to your healthcare provider about safer sex practices.

What are the possible side effects of Imiquimod Cream?
The most common side effects with Imiquimod Cream are skin reactions at the treatment site including:
• redness
• swelling
• a sore, blister, or ulcer
• skin that becomes hard or thickened
• skin peeling
• scabbing and crusting
• itching
• burning
• changes in skin color that do not always go away

Actinic Keratosis
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, scabbing, itching and burning are common at the site where Imiquimod Cream is applied, and sometimes the side effects go outside of the area where Imiquimod Cream was applied. Swelling, small open sores and drainage may also be experienced with use of Imiquimod Cream. You may also experience itching and/or burning. Actinic keratoses that were not seen before may appear during treatment and may later go away. If you have questions regarding treatment or skin reactions, please talk with your healthcare provider.

Superficial Basal Cell Carcinoma
During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects, such as redness, swelling and a sore are common at the site where Imiquimod Cream is applied. You may also experience itching or burning. Your healthcare provider will need to check the area that was treated after your treatment is finished to make sure that the skin cancer is gone. Superficial basal cell carcinoma can come back. The chances of it coming back are higher as time passes. **It is very important to have regular follow-up visits with your healthcare provider to check the area to make sure your skin cancer has not come back. Ask your healthcare provider how often you should have your skin checked.** Talk with your healthcare provider if you have questions about your treatment or skin reactions.

External Genital and Perianal Warts
Patients should be aware that new warts may develop during treatment, as Imiquimod Cream is not a cure. Many people see reddening or swelling on or around the application site during the course of treatment. If you have questions regarding treatment or local skin reactions, please talk with your healthcare provider.

You have a higher chance for severe skin reactions if you use too much Imiquimod Cream or use it the wrong way. **Stop Imiquimod Cream right away and call your healthcare provider if you get any skin reactions that affect your daily activities, or that do not go away.** Sometimes, Imiquimod Cream must be stopped for a while to allow your skin to heal. Talk to your healthcare provider if you have questions about your treatment or skin reactions.

Other side effects of Imiquimod Cream include headache, back pain, muscle aches, tiredness, flu-like symptoms, swollen lymph nodes, diarrhea, and fungal infections.
If the reactions seem excessive, if either skin breaks down or sores develop during the first week of treatment, if flu-like symptoms develop or if you begin to not feel well at anytime, contact your healthcare provider.

These are not all the side effects of Imiquimod Cream. For more information, ask your healthcare provider or pharmacist.

How do I store Imiquimod Cream?
• Store Imiquimod Cream at 39 - 77° F (4 - 25° C). Do not freeze.
• Safely throw away Imiquimod Cream that is out of date or that you do not need.
• **Keep Imiquimod Cream and all medicines out of the reach of children.**

General information about Imiquimod Cream
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Imiquimod Cream for a condition for which it was not prescribed. Do not give Imiquimod Cream to other people, even if they have the same symptoms you have.

This leaflet summarizes the most important information about Imiquimod Cream. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Imiquimod Cream that is written for the healthcare provider.
If you have other questions about Imiquimod Cream, call 1-800-645-9833

What are the ingredients in Imiquimod Cream?
Active Ingredient: imiquimod
Inactive ingredients: oleic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

E. FOUGERA & CO.
A division of Nycomed US Inc.
Melville, New York 11747

IF5386
R2/08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-548

Date of Submission: October 16, 2006

Applicant's Name: Altana

Established Name: Imiquimod Cream, 5%

Labeling Deficiencies:

1. **CONTAINER (Single foil Packet):**
   - Add the statement **"Discard unused** (b) (4) **".**
   - If space permits, you may add the route of administration and storage statement as does the reference listed drug, Aldara.
2. **CARTON (12 single-use packets):**
   - Revise your storage temperature to read as "Store at 4 - 25°C (39 - 77°F)".
   - Replace " (b) (4) " with the statements "For Dermatologic Use Only" and "Not for Ophthalmic Use".
   - Revise " (b) (4) ingredients" to read as "inactive ingredients'
   - Recommend adding the statement "This package is not child resistant"
3. **INSERT:** Revise your package insert labeling to be in accord with the most recently approved labeling for the reference listed drug, Aldara (NDA 20-723/S-020: Approved March 22, 2007). We refer you to http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
4. **PATIENT INFORMATION:** See INSERT Comment.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug insert labeling and a side-by-side comparison of your proposed carton and container labels with your last submission, with all differences annotated and explained

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have Final Printed Labels and Labeling?

Container Labels (Single foil Packet): Satisfactory in final print as of electronic submission.

Carton Labeling (12 single-use packets): Satisfactory in final print as of electronic submission.

Insert Labeling: Satisfactory in final print as of electronic submission.

Patient Information: Satisfactory in final print as of electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Aldara Cream, 5%,
- NDA Number: 20-723
- NDA Drug Name: Imiquimod Cream, 5%
- NDA Firm: 3M Pharmaceuticals
- Date of Approval of NDA Insert: **NDA 20-723/S-020: Approved March 22, 2007**
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparision
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-723

No	Expiration	Use Code	Use	File
4689338	AUG 25,2009	U-172	**TREATMENT OF GENITAL WARTS**	**IV**
4689338*PED	FEB 25,2010			
5238944	AUG 24,2010			**IV**
5238944*PED	FEB 24,2011			

Exclusivity Data For NDA 20-723

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-433	July 14, 2007		TREATMENT OF BIOPSY-CONFIRMED, PRIMARY SUPERFICIAL BASAL CELL CARCINOMA IN IMMUNOCOMPETENT ADULTS, WITH A MAXIMUM TUMOR DIAMETER OF 2.0CM, LOCATED ON THE TRUNK (EXCLUDING ANOGENITAL SKIN), NECK, OR EXTREMITIES (EXCLUDING HANDS AND FEET)	NONE
PED	Jan 14, 2008		PEDIATRIC EXCLUSIVITY	NONE
I-420	March 2, 2007		TOPICAL TREATMENT OF CLINICALLY TYPICAL, NONHYPERKERATOTIC, NONHYPERTROPHIC ACTINIC KERATOSES ON THE FACE OR SCALP IN IMMUNOCOMPETENT ADULTS	NONE
PED	Sep 2, 2007		PEDIATRIC EXCLUSIVITY	NONE

NOTES/QUESTIONS TO THE CHEMIST: Does the firm's stability data support the storage temperature Store at 4 - 25°C (39 - 77°F)?

Answer per chemistry: YES. The firm did a cycling study from 4±2ºC to 40±2ºC and per chemistry the cycling study is acceptable to support the recommended storage temperature "Store at 4 - 25°C (39 - 77°F)".

FOR THE RECORD:

1. **MODEL LABELING:** Review based on the labeling for the reference listed drug, Aldara Cream, 5%, (NDA 20-723/S-020: Approved March 22, 2007). This supplement provides for the addition of pediatric safety data in the **INDICATIONS and USAGE** and **USE IN SPECIFIC POPULATIONS: Pediatric Use** sections of the labeling.

2. **PATIENTS/EXCLUSIVTIES:**

Patent Data – NDA

No	Expiration	Use Code	Use	File
4689338	AUG 25,2009	U-172	**TREATMENT OF GENITAL WARTS**	**IV**
4689338*PED	FEB 25,2010			
5238944	AUG 24,2010			**IV**
5238944*PED	FEB 24,2011			

Exclusivity Data For NDA

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-433	July 14, 2007		TREATMENT OF BIOPSY-CONFIRMED, PRIMARY SUPERFICIAL BASAL CELL CARCINOMA IN IMMUNOCOMPETENT ADULTS, WITH A MAXIMUM TUMOR DIAMETER OF 2.0CM, LOCATED ON THE TRUNK (EXCLUDING ANOGENITAL SKIN), NECK, OR EXTREMITIES (EXCLUDING HANDS AND FEET)	NONE
PED	Jan 14, 2008		PEDIATRIC EXCLUSIVITY	NONE
I-420	March 2, 2007		TOPICAL TREATMENT OF CLINICALLY TYPICAL, NONHYPERKERATOTIC, NONHYPERTROPHIC ACTINIC KERATOSES ON THE FACE OR SCALP IN IMMUNOCOMPETENT ADULTS	NONE
PED	Sep 2, 2007		PEDIATRIC EXCLUSIVITY	NONE

3. **INACTIVE INGREDIENTS**
There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

INGREDIENT	IIG* %	PROPOSED DRUG %
****Oleic Acid**	******	(b) (4)
Cetyl Alcohol, NF	12	
Stearyl Alcohol, NF	30	
White Petrolatum, USP	58.2	
Polysorbate 60, NF	8	
Sorbitan Monostearate, NF	8	
Glycerin, USP	20	
Xantan Gum, NF	0.75	
Purified Water, USP	N/A	
Benzyl Alcohol, NF	2.7	
Methylparaben, NF	18	
Propylparaben, NF	1	

* All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide Database (July 7, 2006)

** See pages 299 to 307 for justification for the addition of (b) (4)% Oleic acid to Imiquimod Cream, 5%.

The package insert (PI) of the Innovator Aldara™ Cream, 5% states that it contains Imiquimod as the active ingredient, and isostearic acid, benzyl alcohol, polysorbate 60, sorbitan monostearate, cetyl alcohol, stearyl alcohol, white petrolatum, propylparaben, purified water, glycerin, methylparaben, and xanthan gum as inactive ingredients.

There are no difference between both the proposed formulation and the RLD with the exception, ALTANA has replaced Isotearic acid with Oleic Acid.

****OGD consult was submitted on 1/29/07 regarding Oleic Acid level in the Cream formulation.**
(b) (4)

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- RLD: Store at 4 - 25°C (39 - 77°F) Avoid freezing.
- ANDA: Store (b) (4) Avoid freezing. Firm was asked to revise their storage temperature to be the same as the RLD.

5. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: Packaged as a 250 mg single-unit (12 single use packets).
- ANDA: The drug product will be packaged in (b) (4) Foil Pack – (b) (4) as a 250 mg single-unit (12 single use packets).

7. CONTAINER/CLOSURE

IMIQUIMOD Cream 5% is packaged as 250 mg single-use in Foil Pack. (b) (4) Foil Pack is a packet (b) (4) .

8. FINSHED DOSAGE FORM

A white to off-white, smooth and homogeneous cream.

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

ALTANA Inc.
55 Cantiague Rock Road
Hicksville, NY 11801

Date of Submission: October 16, 2006

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

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

/s/

Beverly Weitzman
1/9/2008 04:07:25 PM
LABELING REVIEWER

John Grace
1/10/2008 12:48:00 PM
LABELING REVIEWER

APPROVAL SUMMARY #1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-548

Date of Submission: January 22, 2008 and February 13, 2008

Applicant's Name: Altana

Established Name: Imiquimod Cream, 5%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have Final Printed Labels and Labeling? YES

Container Labels (Single foil Packet): Satisfactory in final print as of **January 22, 2008** electronic submission.

\\Cdsesub1\evsprod\ANDA078548\0001\m1\us\final-container.pdf

Carton Labeling (12 single-use packets): Satisfactory in final print as of **January 22, 2008** electronic submission. \\Cdsesub1\evsprod\ANDA078548\0001\m1\us\final-carton.pdf

Insert Labeling: Satisfactory in final print as of **January 22, 2008** electronic submission.

\\Cdsesub1\evsprod\ANDA078548\0001\m1\us\pi.pdf

Patient Information: Satisfactory in final print as of **February 13, 2008** electronic submission.

\\Cdsesub1\evsprod\ANDA078548\0002\m1\us\pi.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Aldara Cream, 5%,
- NDA Number: 20-723
- NDA Drug Name: Imiquimod Cream, 5%
- NDA Firm: 3M Pharmaceuticals
- Date of Approval of NDA Insert: **NDA 20-723/S-020: Approved March 22, 2007**
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparision
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-723

No	Expiration	Use Code	Use	File
4689338	AUG 25,2009	U-172	**TREATMENT OF GENITAL WARTS**	**IV**
4689338*PED	FEB 25,2010			
5238944	AUG 24,2010			**IV**
5238944*PED	FEB 24,2011			

Exclusivity Data For NDA 20-723

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-433	July 14, 2007		TREATMENT OF BIOPSY-CONFIRMED, PRIMARY SUPERFICIAL BASAL CELL CARCINOMA IN IMMUNOCOMPETENT ADULTS, WITH A MAXIMUM TUMOR DIAMETER OF 2.0CM, LOCATED ON THE TRUNK (EXCLUDING ANOGENITAL SKIN), NECK, OR EXTREMITIES (EXCLUDING HANDS AND FEET)	NONE
PED	Jan 14, 2008		PEDIATRIC EXCLUSIVITY	NONE
I-420	March 2, 2007		TOPICAL TREATMENT OF CLINICALLY TYPICAL, NONHYPERKERATOTIC, NONHYPERTROPHIC ACTINIC KERATOSES ON THE FACE OR SCALP IN IMMUNOCOMPETENT ADULTS	NONE
PED	Sep 2, 2007		PEDIATRIC EXCLUSIVITY	NONE

NOTES/QUESTIONS TO THE CHEMIST: Does the firm's stability data support the storage temperature Store at 4 - 25°C (39 - 77°F)?

Answer per chemistry: YES. The firm did a cycling study from 4±2ºC to 40±2ºC and per chemistry the cycling study is acceptable to support the recommended storage temperature "Store at 4 - 25°C (39 - 77°F)".

FOR THE RECORD:

1. **MODEL LABELING:** Review based on the labeling for the reference listed drug, Aldara Cream, 5%, (NDA 20-723/S-020: Approved March 22, 2007). This supplement provides for the addition of pediatric safety data in the **INDICATIONS and USAGE** and **USE IN SPECIFIC POPULATIONS: Pediatric Use** sections of the labeling.

2. **PATIENTS/EXCLUSIVTIES:**

Patent Data – NDA

No	Expiration	Use Code	Use	File
4689338	AUG 25,2009	U-172	**TREATMENT OF GENITAL WARTS**	**IV**
4689338*PED	FEB 25,2010			
5238944	AUG 24,2010			**IV**
5238944*PED	FEB 24,2011			

Exclusivity Data For NDA

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-433	July 14, 2007		TREATMENT OF BIOPSY-CONFIRMED, PRIMARY SUPERFICIAL BASAL CELL CARCINOMA IN IMMUNOCOMPETENT ADULTS, WITH A MAXIMUM TUMOR DIAMETER OF 2.0CM, LOCATED ON THE TRUNK (EXCLUDING ANOGENITAL SKIN), NECK, OR EXTREMITIES (EXCLUDING HANDS AND FEET)	NONE
PED	Jan 14, 2008		PEDIATRIC EXCLUSIVITY	NONE
I-420	March 2, 2007		TOPICAL TREATMENT OF CLINICALLY TYPICAL, NONHYPERKERATOTIC, NONHYPERTROPHIC ACTINIC KERATOSES ON THE FACE OR SCALP IN IMMUNOCOMPETENT ADULTS	NONE
PED	Sep 2, 2007		PEDIATRIC EXCLUSIVITY	NONE

3. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

INGREDIENT	IIG* %	PROPOSED DRUG %
****Oleic Acid**	******	(b) (4)
Cetyl Alcohol, NF	12	
Stearyl Alcohol, NF	30	
White Petrolatum, USP	58.2	
Polysorbate 60, NF	8	
Sorbitan Monostearate, NF	8	
Glycerin, USP	20	
Xantan Gum, NF	0.75	
Purified Water, USP	N/A	
Benzyl Alcohol, NF	2.7	
Methylparaben, NF	18	
Propylparaben, NF	1	

* All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide Database (July 7, 2006)

** See pages 299 to 307 for justification for the addition of (b)(4)% Oleic acid to Imiquimod Cream, 5%.

The package insert (PI) of the Innovator Aldara™ Cream, 5% states that it contains Imiquimod as the active ingredient, and isostearic acid, benzyl alcohol, polysorbate 60, sorbitan monostearate, cetyl alcohol, stearyl alcohol, white petrolatum, propylparaben, purified water, glycerin, methylparaben, and xanthan gum as inactive ingredients.

There are no difference between both the proposed formulation and the RLD with the exception, ALTANA has replaced Isotearic acid with Oleic Acid.

****OGD consult was submitted on 1/29/07 regarding Oleic Acid level in the Cream formulation.**

(b) (4)

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- RLD: Store at 4 - 25°C (39 - 77°F) Avoid freezing.
- ANDA: Store (b) (4) Avoid freezing. Firm was asked to revise their storage temperature to be the same as the RLD.

5. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: Packaged as a 250 mg single-unit (12 single use packets).
- ANDA: The drug product will be packaged in (b) (4) Foil Pack – (b) (4) as a 250 mg single-unit (12 single use packets).

7. CONTAINER/CLOSURE

IMIQUIMOD Cream 5% is packaged as 250 mg single-use in Foil Pack. (b) (4) Foil Pack is a packet (b) (4).

8. FINSHED DOSAGE FORM

A white to off-white, smooth and homogeneous cream.

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

ALTANA Inc.
55 Cantiague Rock Road
Hicksville, NY 11801

Date of Submission: January 22, 2008 and February 13, 2008

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

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

/s/

Beverly Weitzman
2/14/2008 09:19:08 AM
LABELING REVIEWER

John Grace
2/15/2008 06:09:25 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

CHEMISTRY REVIEWS

ANDA 78 - 548

Imiquimod Cream, 5%

Altana Inc.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-548

2. REVIEW #: 1

3. REVIEW DATE: 1/25/07

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	10/16/06
Acceptable for filing	10/17/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Inc.
Address:	P.O. Box 2006, 60 Baylis Road Melville, NY 11747
Representative:	Robert J. Anderson
Telephone:	631-454-7677

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Imiquimod Cream, 5%

9. LEGAL BASIS FOR SUBMISSION:

The firm submitted paragraph III and IV certifications.

Altana Inc certifies that to the best of its knowledge, the patents for the listed drug product ALDARA™ (Imiquimod) Cream, 5% will expire as indicated below:

Patent Number	Patent Expires
4,689,338 ("the '338 Patent")	August 25, 2009
5,238,944 ("the '944 Patent")	August 24, 2010

To the best of Altana's knowledge, 3M is the holder of the approved application NDA 20-723 for the drug product, and 3M or its subsidiary, 3M Innovative Properties Company, is the owner of record of the '338 Patent and the '944 Patent.

Paragraph III Certification.

Altana certifies that in its opinion and to its best knowledge the '338 Patent will expire on August 25, 2009.

Paragraph IV Certification.

ALTANA certifies that in its opinion and to its best knowledge none of the claims of the '944 Patent will be infringed by the commercial manufacture, use or sale of ALTANA's proposed product ("the Proposed Product") for which this application is submitted.

ALTANA does not concede that any of the claims of the'338 Patent or '944 Patent are valid or enforceable and does not concede that any of the claims of the '338 Patent would be infringed by the commercial manufacture, use or sale of the Proposed Product.

ALTANA expressly reserves the right to challenge the validity and enforceability of the '338 Patent and the '944 Patent and/or make other arguments relating to infringement.

ALTANA further certifies that notice to the owner of the patents and to the NDA holder required will be sent by certified mail, return receipt requested. Concurrently with sending the aforementioned notice to the NDA holder and patent owner, ALTANA will amend its ANDA for Imiquimod Cream, 5% to include a certification that the requisite notice has been provided.

Exclusivity Statement:

The Orange Book currently states that the product has market exclusivity under exclusivity codes I-433 and I-420 and that such exclusivity will expire July 14, 2007 and March 2, 2007, respectively.

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

10. PHARMACOL CATEGORY:

Antiviral agent, used as an immunomodulator

11. DOSAGE FORM:

Cream

12. STRENGTH/POTENCY:

5%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

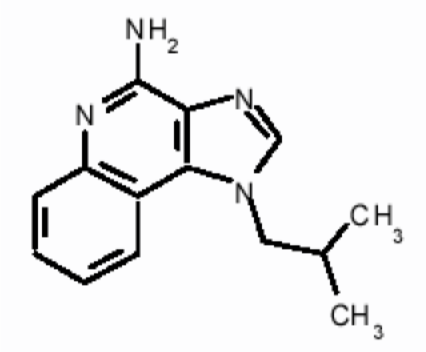
_____SPOTS product – Form Completed

__XX___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula $C_{14}H_{16}N_4$ Molecular Weight 240.3



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	3/9/07	By N. Nashed
	III			4			
	III			4			

NOTE:

* ALTANA is currently seeking approval of (b) (4) **only**.

The (b) (4) is no longer commercially available.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78 -548

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product will be packaged in [redacted] (b) (4) Foil Pack – [redacted] (b) (4) as a 250 mg single-unit.

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

The drug substance is a white to off-white crystalline powder with empirical formula $C_{14}H_{16}N_4$ and molecular weight 240.3.

In terms of chemistry ALDARA™ and IMIQUIMOD both are cream.

IMIQUIMOD Cream consist of Oleic acid, Cetyl alcohol, Stearyl alcohol, White petrolatum, Polysorbate 60, Glycerin, Sorbitan monostearate, benzyl alcohol, Propylparaben, Methylparaben, Xanthan gum.

B. Description of How the Drug Product is Intended to be Used

IMIQUIMOD Cream 5% is indicated for topical treatment of actinic keratoses on the face or scalp, primary superficial basal cell carcinoma (sBCC) and external genital and perianal warts/condyloma acuminate.

ALTANA Maximum Daily Dose (MDD):

Superficial basal cell carcinoma basal cell carcinoma would be the indication that requires the largest amount of the drug per application. For this indication the drug is applied 5 times per week for 6 weeks. The target tumor should have a maximum diameter of no more than 2 cm with an approximate amount of 40 mg of cream to be used. The absorption rate (as eliminated imquimod) was in the range of 0.08%-2.41%, with the highest absorption rate corresponding to female patients treated for gentital/perianal warts. Absorption of Imiquimod from the applied dose= 2.41% (worst case scenario).

40 mg x 1 application/day = 40 mg of Imquimod Cream 5% per day
(worst case scenario).

Maximum Daily Dose (MDD) = 40 mg/day x 2.41 x 50 mg/g = 0.048 mg/day

DS: (IT) = 0.10% (QT) = 0.15%

DP: (IT) = 1.0% (QT) = 1.0%

Storage Condition:

Store [redacted] (b) (4). Avoid Freezing.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to minor deficiencies.

Following this page, 22 pages withheld in full - (b)(4)

NOTE:

(b) (4)

NOTE:

ALTANA stated will place the first three batches of IMIQUIMOD Cream 5% on stability (b) (4)

Deficiencies:

Please provide (b) (4) the finished drug product IMIQUIMOD Cream 5%.

Please revise your (b) (4)

30. MICROBIOLOGY

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Not required.

32. LABELING

Pending

33. ESTABLISHMENT INSPECTION

Pending

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

ALTANA claims a categorical exclusion under 21 CFR 25.31.

The firm certifies that to its best knowledge, the locations where the product will be produced, used and disposed of are in substantial compliance with all applicable federal, state and local environment laws.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78 - 548 APPLICANT: ALTANA Inc.

DRUG PRODUCT: IMIQUIMOD Cream 5%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide a [redacted] (b) (4)

2. Please provide information regarding the [redacted] (b) (4)

3. Please provide a [redacted] (b) (4)

4. Please provide a comparison between the [redacted] (b) (4)

5. Please provide the [redacted] (b) (4)
.

6. Please continue performing [redacted] (b) (4)

7. Please provide information regarding [redacted] (b) (4)

8. Please revise your specifications for the [redacted] (b) (4)

9. Please provide [redacted] (b) (4) drug product IMIQUIMOD Cream 5%.

10. Please revise your [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please refer to the telephone conference between the agency and Altana Inc. that occurred on March 13, 2007 regarding the calculation of the maximum daily dosage (MDD) of your drug product. Please revise and correct the MDD calculations in all applicable sections of your application.

2. The firms referenced in your application should be in compliance with CGMP at the time of approval.

3. Please provide all available drug product stability data.

4. The bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

5. The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

Rasmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-548
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed

HFD-620/P.Schwartz

HFD-617/R.Adigun

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

/s/

Nashed Nashed
3/16/2007 10:41:50 AM
CHEMIST

Rosalyn Adigun
3/20/2007 03:47:01 PM
CSO

Paul Schwartz
3/20/2007 03:54:57 PM
CHEMIST
Signed for R. Patel

ANDA 78 - 548

IMIQUIMOD Cream, 5%

ALTANA INC.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-548

2. REVIEW #: 1 (QbR-QOS)

It is acknowledged in Chemistry Review #3 that this was a numbering error. This is Chemistry Review #2.

3. REVIEW DATE: 6/19/07
Revised: 7/21/07

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	10/16/06
Acceptable for filing	10/17/06
New correspondence	10/19/06
Amendment – Reviewer Aid (additional toxicology summaries)	12/4/06
Telephone Amendment	1/9/07
Telephone Amendment	1/11/07
Minor Amendment (CMC) – Response to Chemistry Deficiencies Letter dated March 20, 2007	3/30/07
Telephone Amendment-Requested Information	5/11/07
Telephone Amendment (CMC)	5/30/07

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Inc.
Address:	P.O. Box 2006 60 Baylis Road Melville, NY 11747
Representative:	Robert J. Anderson
Telephone:	631-454-7677

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): IMIQUIMOD Cream, 5%

9. LEGAL BASIS FOR SUBMISSION:

The firm submitted paragraph III and IV certifications.
Altana Inc certifies that to the best of its knowledge there are two patents are listed for the drug product ALDARA™ (Imiquimod) Cream, 5% will and expire as indicated below:

Patent Number	Patent Expires
4,689,338 ("the '338 Patent")	August 25, 2009
5,238,944 ("the '944 Patent")	August 24, 2010

To the best of Altana's knowledge, 3M is the holder of the approved application NDA 20-723 for the drug product, and 3M or its subsidiary, 3M Innovative Properties Company, is the owner of record of the '338 Patent and the '944 Patent.

Paragraph III Certification.

Altana certifies that in its opinion and to its best knowledge the '338 Patent will expire on August 25, 2009.

Paragraph IV Certification.

ALTANA certifies that in its opinion and to its best knowledge none of the claims of the '944 Patent will be infringed by the commercial manufacture, use or sale of ALTANA's proposed product ("the Proposed Product") for which this application is submitted.

ALTANA does not concede that any of the claims of the'338 Patent or '944 Patent are valid or enforceable and does not concede that any of the claims of the '338 Patent would be infringed by the commercial manufacture, use or sale of the Proposed Product.

ALTANA expressly reserves the right to challenge the validity and enforceability of the '338 Patent and the '944 Patent and/or make other arguments relating to infringement.

ALTANA further certifies that notice to the owner of the patents and to the NDA holder required will be sent by certified mail, return receipt requested. Concurrently with sending the aforementioned notice to the NDA holder and patent owner, ALTANA will amend its ANDA for Imiquimod Cream, 5% to include a certification that the requisite notice has been provided.

Exclusivity Statement:

The Orange Book currently states that the product has market exclusivity under exclusivity codes I-433 and I-420 and that such exclusivity will expire July 14, 2007 and March 2, 2007, respectively.

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

10. PHARMACOL CATEGORY:

Antiviral agent, used as an immunomodulator

11. DOSAGE FORM:

Cream

12. STRENGTH/POTENCY:

5%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

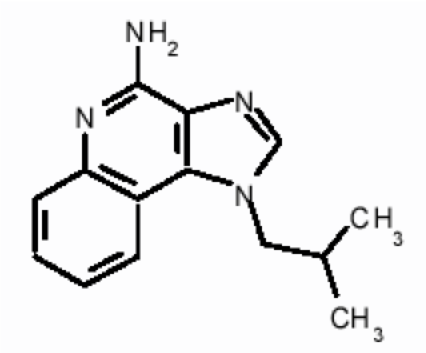
_____SPOTS product – Form Completed

__XX___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula $C_{14}H_{16}N_4$ Molecular Weight 240.3



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	3/12/07	By N. Nashed
	III			4			
	III			4			

NOTE:

* ALTANA is currently seeking approval of (b) (4) **only**.

The (b) (4) is no longer commercially available.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _XX___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78 - 548

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product will be packaged in (b) (4) Foil Pack – (b) (4) as a 250 mg single-unit.

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

The drug substance is a white to off-white crystalline powder with empirical formula $C_{14}H_{16}N_4$ and molecular weight 240.3.

In terms of chemistry ALDARA™ and IMIQUIMOD both are cream.

IMIQUIMOD Cream consist of Oleic acid, Cetyl alcohol, Stearyl alcohol, White petrolatum, Polysorbate 60, Glycerin, Sorbitan monostearate, benzyl alcohol, Propylparaben, Methylparaben, Xanthan gum.

B. Description of How the Drug Product is Intended to be Used

IMIQUIMOD Cream 5% is indicated for topical treatment of actinic keratoses on the face or scalp in immunocompetent adults, for superficial basal cell carcinoma in immunocompetent adults, and for external genital and perianal warts/condyloma acuminate in individuals 12 years old and above.

ALTANA Maximum Daily Dose (MDD):

The absorption rate (as eliminated imquimod) was in the range of 0.08%-2.41%, with the highest absorption rate corresponding to female patients treated for gentital/perianal warts.

Absorption of Imiquimod from the applied dose= 2.41% (worst case scenario).

IMIQUIMOD Cream 5% is packaged in a single use packets, which contain 250 mg of the drug product.

250 mg X 1 application/day = 250 mg/day of Imiquimod Cream 5% per day (worst case scenario)

Maximum daily dose (MDD) = 250 mg/day X 5% X 2.41% = 0.30125 mg/day

DS: (IT) = 0.10% (QT) = 0.15%

DP: (IT) = 0.5% (QT) = 1.0%

Storage Condition:

Store below 25ºC (77ºF). Avoid Freezing.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to minor deficiencies.

Following this page, 103 pages withheld in full - (b)(4)

Executed Production Record

The executed production batch records for the Imiquimod Cream 5% drug product can be found in Volume 1.5, Section 3.2. R, pages 1334 to 1747.

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory

ALTANA claims a categorical exclusion under 21 CFR 25.31.

The firm certifies that to its best knowledge, the locations where the product will be produced, used and disposed of are in substantial compliance with all applicable federal, state and local environment laws.

ANDA: 78 - 548 APPLICANT: ALTANA Inc.

DRUG PRODUCT: IMIQUIMOD Cream 5%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide an additional (b) (4)

2. Please provide a statement (b) (4)

3. Please revise the (b) (4)

4. Please qualify your (b) (4)

5. Please be advised that any revisions made to the (b) (4)

6. Please provide a list of the (b) (4) for example:

- (b) (4)
-
-
-
-

(b) (4)

7. Please provide answer for these questions.

How were the (b) (4) (b) (4)?

What is the (b) (4)?

8. Please specify the (b) (4) is not acceptable.

9. Please revise your (b) (4)

10. (b) (4)

11. Please provide a (b) (4) of the drug product.

12. Please revise your (b) (4)

Chemistry Assessment Section

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-548
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed

HFD-620/P.Schwartz

HFD-617/R.Adigun

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

/s/

Nashed Nashed
7/27/2007 07:14:13 AM
CHEMIST

Rosalyn Adigun
7/27/2007 03:58:34 PM
CSO

Paul Schwartz
7/30/2007 03:34:16 PM
CHEMIST

Chemistry Review Data Sheet

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ANDA 78 - 548

IMIQUIMOD Cream, 5%

NYCOMED US INC.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-548

2. REVIEW #: 3 (QbR-QOS)

3. REVIEW DATE: 8/29/08 by Nashed Nashed
   Revised: 5/12/09 by Nashed Nashed
   Updated: 1/19/2010 by Bing Cai

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	10/16/06
Acceptable for filing	10/17/06
New correspondence	10/19/06
Amendment –(additional toxicology summaries)	12/4/06
Telephone Amendment	1/9/07
Telephone Amendment	1/11/07
CMC NA Minor/CR#1	**3/20/07**
Minor Amend/Response to Chem Def 03/20/07	3/30/07
Telephone Amendment-Requested Information	5/11/07
Telephone Amendment (CMC)	5/30/07
CMC NA Minor/CR2*	**7/30/07**

*Review dated 7/30/2007 (CR#2) was incorrectly numbered as CR#1

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (CMC)	10/2/07
Labeling Amendment	1/22/08
Gratuitous Amendment (CMC)	6/12/08
Telephone Amendment (CMC)	7/25/08
Telephone Amendment (CMC)	8/15/08
Telephone Amendment (CMC)	8/22/08
Telephone Amendment (CMC)	8/28/08
Telephone Amendment (CMC)	3/13/09
Telephone Amendment (CMC)	1/20/10

7. NAME & ADDRESS OF APPLICANT:

Name: NYCOMED US INC.

Address: P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Representative: Robert J. Anderson, Esq.
Vice President, Scientific Affairs

Telephone: 631-454-7677

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): IMIQUIMOD Cream, 5%

9. LEGAL BASIS FOR SUBMISSION:

The firm submitted paragraph III and IV certifications.
Nycomed Inc certifies that to the best of its knowledge there are two patents are listed for the drug product ALDARA™ (Imiquimod) Cream, 5% will and expire as indicated below:

Patent Number	Patent Expires
4,689,338 ("the '338 Patent")	August 25, 2009
5,238,944 ("the '944 Patent")	August 24, 2010

To the best of Nycomed's knowledge, 3M is the holder of the approved application NDA 20-723 for the drug product, and 3M or its subsidiary, 3M Innovative Properties Company, is the owner of record of the '338 Patent and the '944 Patent.

Paragraph III Certification.

Nycomed certifies that in its opinion and to its best knowledge the '338 Patent will expire on August 25, 2009.

Paragraph IV Certification.

Nycomed certifies that in its opinion and to its best knowledge none of the claims of the '944 Patent will be infringed by the commercial manufacture, use or sale of Nycomed's proposed product ("the Proposed Product") for which this application is submitted.

Nycomed does not concede that any of the claims of the'338 Patent or '944 Patent are valid or enforceable and does not concede that any of the claims of the '338 Patent would be infringed by the commercial manufacture, use or sale of the Proposed Product.

Nycomed expressly reserves the right to challenge the validity and enforceability of the '338 Patent and the '944 Patent and/or make other arguments relating to infringement.

Nycomed further certifies that notice to the owner of the patents and to the NDA holder required will be sent by certified mail, return receipt requested. Concurrently with sending the aforementioned notice to the NDA holder and patent owner, ALTANA will amend its ANDA for Imiquimod Cream, 5% to include a certification that the requisite notice has been provided.

Exclusivity Statement:

The Orange Book currently states that the product has market exclusivity under exclusivity codes I-433 and I-420 and that such exclusivity will expire July 14, 2007 and March 2, 2007, respectively.

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

10. PHARMACOL CATEGORY:

Antiviral agent, used as an immunomodulator

11. DOSAGE FORM:

Cream

12. STRENGTH/POTENCY:

5%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

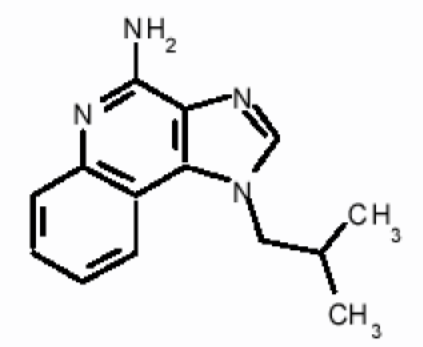
_____SPOTS product – Form Completed

__XX___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula $C_{14}H_{16}N_4$ Molecular Weight 240.3



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	1/19/2010	By B. Cai
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES*	Acceptable/	4/1/09	
Methods Validation	Not required		
Labeling	Acceptable	2/15/08	B. Weitzman
Bioequivalence	Acceptable	1/26/2010	Brenda Gierhart, Carol Kim
EA	Not required		
Radiopharmaceutical	N/A		
Oleic Acid ((b) (4) as Excipient in Imiquimod Cream Nycomed (5%) ANDA 78-548	Acceptable	2/13/09	Robert T. Dorsam, Ph.D.

***See current list in the amendment dated 1/20/2010.**

(b) (4) MO submitted to EES and found acceptable on 1/25/2010.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes XX____ No If no, explain reason(s) below:

The application is Minor

The Chemistry Review for ANDA 78 - 548

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Consult of Oleic Acid ((b) (4) as excipients in Nycomed Imiquiod Cream 5% is acceptable for Pharm./Tox. on February 13, 2009 by Robert T. Dorsam, Ph.D.

The firm provided adequate, acceptable, and satisfactory information for all the excipients and the drug substance regarding the USP <467> residual solvents requirements.

The application is approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product will be marketed as a 250 mg single unit in (b) (4) Foilpac (b) (4) and (b) (4).

The Reference Listed Drug (RLD) is ALDARA™ (Imiquimod) Cream, 5% by 3M Pharmaceuticals, the holder of NDA 20-723.

The drug substance is a white to off-white crystalline powder with empirical formula $C_{14}H_{16}N_4$ and molecular weight 240.3.

In terms of chemistry ALDARA™ and IMIQUIMOD both are cream.

IMIQUIMOD Cream consist of Oleic acid, Cetyl alcohol, Stearyl alcohol, White petrolatum, Polysorbate 60, Glycerin, Sorbitan monostearate, benzyl alcohol, Propylparaben, Methylparaben, Xanthan gum.

B. Description of How the Drug Product is Intended to be Used

IMIQUIMOD Cream 5% is indicated for topical treatment of actinic keratoses on the face or scalp in immunocompetent adults, for superficial basal cell carcinoma in immunocompetent adults, and for external genital and perianal warts/ condyloma acuminate in individuals 12 years old and above.

Maximum Daily Dose (MDD):

The absorption rate (as eliminated imquimod) was in the range of 0.08%-2.41%, with the highest absorption rate corresponding to female patients treated for gentital/perianal warts.

Absorption of Imiquimod from the applied dose= 2.41% (worst case scenario).

IMIQUIMOD Cream 5% is packaged in a single use packets, which contain 250 mg of the drug product.

250 mg X 1 application/day = 250 mg/day of Imiquimod Cream 5% per day (worst case scenario)

Maximum daily dose (MDD) = 250 mg/day X 5% X 2.41% = 0.30125 mg/day

DS: (IT) = 0.10% (QT) = 0.15%

DP: (IT) = 0.5% (QT) = 1.0%

Storage Condition:

Store below 25ºC (77ºF). Avoid Freezing.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

Following this page, 122 pages withheld in full - (b)(4)

ALTANA provided a table (b) (4) [redacted] o the proposed drug product.

ALTANA stated that based on the data provided in Volume 1.4, (b) (4) [redacted]

ALTANA is proposing (b) (4) [redacted] in the Minor Amendment dated 3/30/07.

The testing results of this product meets the requirements of the current USP test and found to be satisfactory.

ALTANA stability protocol and post-Approval commitments are adequate, acceptable and satisfactory.

30. MICROBIOLOGY

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Not required.

32. LABELING: Satisfactory

Labeling is acceptable on 2/15/08 by B. Weitzman

33. ESTABLISHMENT INSPECTION: Satisfactory

EER is acceptable on April 1, 2009

34. BIOEQUIVALENCE: Acceptable

Acceptable on 1/26/2010

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

ALTANA claims a categorical exclusion under 21 CFR 25.31.

The firm certifies that to its best knowledge, the locations where the product will be produced, used and disposed of are in substantial compliance with all applicable federal, state and local environment laws.

cc: ANDA 78-548
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed

HFD-620/B.Cai

HFD-617/E.Chuh

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78548	ORIG-1	NYCOMED US INC	IMIQUIMOD

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

/s/

NASHED E NASHED
02/24/2010

BING CAI
02/24/2010

EUNJUNG E CHUH
02/24/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

BIOEQUIVALENCE REVIEWS

Review of a Bioequivalence Study with a Clinical Endpoint

ANDA # 78-548 Nycomed US Inc. (formerly Altana, Inc.)

Imiquimod Cream, 5%

Carol Y. Kim, Pharm.D.
Clinical Review Team

Submission dates reviewed:
10/16/06, 4/27/07, & 3/31/08

Date of Review: 1/25/10

Table of Contents

Review of a Bioequivalence Study with a Clinical Endpoint for ANDA 78-548

Executive Summary

This double-blind, randomized, placebo-controlled, multi-center, parallel-group study in the treatment of actinic keratoses (AK) demonstrates that Nycomed US Inc.'s (formerly known as Altana Inc.) Imiquimod Cream, 5%, is bioequivalent to the reference listed drug (RLD), Graceway Pharmaceuticals, LLC's[1] Aldara® Cream, 5%. The FDA statistical review, following adjustment in the per protocol population, concludes that the 90% Confidence Interval (CI) of the difference in success (complete clearance of AK lesions) rate between the test and reference products at the 8-week follow-up (visit 6/week 24) is (-0.094, +0.078), within the bioequivalence limits of (-0.20 to +0.20). Both the test and reference products are shown to be statistically superior to vehicle ($p<0.001$) at visit 6 in the modified intent-to-treat population, demonstrating that the study is sufficiently sensitive to discriminate differences between products. A total of 564 patients were enrolled and randomized. Based on the FDA statistical review, 547 patients were included in the Modified Intent-to-Treat (MITT) population[2] and 474 were included in the Per Protocol (PP) population[3].

I. Recommendation on Approval

The data submitted to ANDA 78-548 are adequate to demonstrate bioequivalence of Nycomed US Inc.'s (Nycomed's) Imiquimod Cream, 5%, with the reference listed drug, Graceway Pharmaceuticals' Aldara® Cream, 5%. The 90% Confidence Interval (CI) of the difference in success rate between the test and reference products at the 8-week follow-up (week 24) is (-0.094,+0.078), within the bioequivalence limits of (-0.20 to +0.20). The test and reference products are also superior to vehicle at week 24 ($p<0.001$), demonstrating that the study is sufficiently sensitive to detect differences between products. Therefore, the Clinical Review Team concludes that the study is adequate to support approval of the application.

II. Summary of Clinical Findings

The data presented in this ANDA 78-548 are adequate to demonstrate that Nycomed's Imiquimod Cream, 5%, is bioequivalent to the reference listed drug, Graceway Pharmaceuticals' Aldara® Cream, 5%, using the primary endpoint of complete clearance of AK lesions (zero clinically visible) in the treated area at visit 6/week 24.

---

[1] On December 29, 2006, Graceway Pharmaceuticals, LLC acquired 3M's Aldara Cream, 5%.

[2] ITT: 1) enrolled and randomized into the study 2) received at least one application of study treatment.
MITT: 1) enrolled into the study, 2) had 4-10 definite, visible, discrete, nonhyperkeratotic, nonhypertrophic, clinically diagnosed AK lesions 3) received at least one application of study medication, 4) had at least one post-baseline efficacy evaluation.

[3] PP: 1) enrolled into the study and met inclusion/exclusion criteria, 2) took between 70%-120% of expected study medication applications, 3) had not taken any concomitant medications that could potentially affect the study evaluations or had any other significant protocol violations, 4) did not miss greater than 6 consecutive study medication applications, 5) returned for visit 6 within the visit windows and had data for all clinical evaluations or 6) met PP criteria up to the time of early study discontinuation due to treatment failure after applying study medication for at least 12 weeks (with a compliance rate of 70%).

A. Brief Overview of Clinical Program

Study #ALT 0432-01-01 was a randomized, double-blind, placebo-controlled, comparative study of Nycomed's Imiquimod Cream, 5%, versus the reference listed drug, Graceway Pharmaceuticals' Aldara® Cream, 5%, in the treatment of AK. Five hundred sixty four (564) patients with AK were randomized in a 3:3:1 ratio to receive the test, reference, or placebo/vehicle cream two times per week for 16 weeks.

B. Comparative Efficacy

The primary endpoint of this study evaluated by the sponsor was the complete clearance of AK lesions in the treated area at the 8-week follow-up (Visit 6, week 24) after completion of 16 weeks of treatment. According to the FDA statistical review, the success rate in the Per-Protocol Population (PP) at visit 6 was 42% in the test group and 43% in the reference group. The 90% CI of the difference in success rate between the two active products is (-0.094,+0.078), which is within the established bioequivalence limits of (-0.20 to +0.20).

C. Comparative Safety

The safety data submitted in this ANDA confirm that the test product did not cause any worse adverse events compared to the reference product in the treatment of actinic keratoses.

A total of 224 patients (94 in the test, 104 in the reference, and 26 in the vehicle group) experienced one or more treatment-emergent adverse events and 9 patients discontinued the study due to an adverse event.

Skin-related adverse events, regardless of relationship to the study medication, occurred in 24 (10%) patients in the test group, 29 (12%) in the reference group, and 5 (6.1%) in the vehicle group. Skin-related adverse events, probably or definitely related to study medication, occurred in 5 patients (2.1%) in the test group, 6 (2.5%) in the reference group, and none in the vehicle group. According to the sponsor's analysis, the difference between the test and reference group with regard to the occurrence of skin-related adverse event was not statistically significant ($p \geq 0.488$).

No deaths occurred in the study. Fifteen serious adverse events were experienced by 13 patients (7 test, 6 reference) in the study but were judged by the sponsor to be unrelated to the study medication.

Clinical Review

I. Introduction and Background

Aldara® (imiquimod 5%) Cream is an immune response modifier approved for the treatment of actinic keratoses (AK), superficial basal cell carcinoma (sBCC), and external genital warts/condyloma acuminata. The mechanism of action of Aldara® Cream for the treatment of AK and sBCC lesions is unknown.

According to the approved labeling, systemic absorption of imiquimod appears to be minimal when used for the approved indications. In a study of 58 patients with AK, the following mean peak imiquimod concentrations were observed after 16 weeks of 3 applications per week: 3.5 ng/mL using 75 mg doses (6 packets) applied to the hands and arms, compared to 0.1 ng/mL using doses of 12.5 mg (1 packet) to the face and 0.2 ng/mL using doses of 25 mg (2 packets) to the scalp. Following 3 applications per week for 16 weeks, mean urinary recoveries of imiquimod and metabolites combined were 0.08 and 0.15% of the applied dose for males and females, respectively, in the group using 75 mg. Systemic exposure appears to be more dependent on surface area of application than the total amount of the applied dose. Mean peak drug concentration of approximately 0.4 ng/ml was observed in 12 patients treated for genital/perianal warts with an average dose of 4.6 mg.

Most patients using Aldara® Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with the recommended treatment regimen.

A. Drug Established Name, Drug Class

Drug Established Name: Imiquimod Cream, 5%
Drug Class: Immune response modifier

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Aldara® (imiquimod) 5% Cream (NDA 20-723), Graceway Pharmaceuticals
Date of approval: 2/27/97
Approved indication(s) based on label approved on 3/22/07: For the topical treatment of:

1) clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults,
2) biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured, and
3) external genital and perianal warts/condyloma acuminata in patients 12 years old or older.

Recommended dosing regimens: The application frequency of Aldara® Cream is different for each indication. For the treatment of AK, the cream should be applied 2 times a week for a full 16 weeks to a defined treatment area on the face or scalp (but not both concurrently).

C. Regulatory Background

The following submissions have been reviewed by the OGD for imiquimod topical cream for conducting a bioequivalence study with a clinical endpoint:

1. INDs, Protocols (P), and/or Control Documents (CD) submitted by Nycomed US Inc. (formerly known as Altana Inc.)

Submission	Submission date	Comment
P04-034	6/23/04	Recommended a BE study in the treatment of AK

2. INDs, Protocols (P), and/or Control Documents (CD) submitted by other sponsors

Submission	Submission date	Sponsor
P04-022	4/16/04	(b) (4)
CD04-381	4/22/04	Teva
P04-040	8/6/04	Taro
CD04-1158	12/2/04	(b) (4)
P07-018	1/27/07 (review pending)	

3. Previous ANDA submissions for the same or related products

None

D. Other Relevant Information

The OGD recommended that this sponsor (P04034, formerly known as Altana Inc.) conduct a bioequivalence study with a clinical endpoint in the treatment of actinic keratoses (AK) for demonstrating bioequivalence of a generic imiquimod to the RLD.

The treatment of AK is preferred over the other approved indications for the assessment of bioequivalence of a generic topical imiquimod cream to the RLD. The clinical presentation of AK is straightforward, and clinical assessment is appropriate and reliable without the need for diagnostic biopsies at baseline or end of treatment. The recommended treatment regimen, including duration of treatment, is the same for all patients. The cure rate is also lower than that for the other indications, suggesting greater sensitivity of the study to discriminate differences between the test and reference products.

For the treatment of external genital warts and perianal warts/condyloma acuminata, the recommended treatment duration is variable, with the treatment being stopped at the time of complete clearance. The duration of treatment for this indication may vary from 9 to 16 weeks based on the reported median time to complete clearance of warts.[4] Furthermore, the NDA studies showed a significantly higher cure rate in females than in males, likely related to differences in the genital skin, or to the degree of occlusion of the application site. These factors are likely to confound a bioequivalence study using this treatment indication. Genital and perianal warts are also predominantly exophytic lesions, protruding from the surface of the skin, whereas the other indications occur in the lower epithelium below the stratum corneum.

[4] The median time for clearance of warts was 10 weeks for 5% imiquimod group and 12 weeks for vehicle group in 1004-IMIQ study and 9 weeks for both active and vehicle group in 1005-IMIQ study, respectively.

Imiquimod is also effective for sBCC, but the cure rates are higher, suggesting that this treatment indication would be less discriminatory in detecting differences between the test and reference products. sBCC is also a more complicated condition to diagnose and evaluate because of the potential for other types of basal cell carcinoma (for which imiquimod is not known to be effective) to exist below the epithelium and not be apparent. Furthermore, as noted above, imiquimod is considered a second line therapy for this indication, to be used only when surgical management is impractical.

Therefore, the OGD recommends a single bioequivalence study with a clinical endpoint in the treatment of AK for the assessment of bioequivalence of generic imiquimod products to the RLD.

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was performed by 15 investigators at 15 sites. Dr. (b) (4) was assigned site number 01 but he did not participate in the study.

Site Number	Principal Investigator	Randomized	Per-Protocol Analyses[1]	Modified Intent-to-Treat Analyses[1]	Intent-to-Treat Analyses[2]
2	Raza Aly, PhD	56	40	55	56
3	Michelle Chambers, MD	19	16	18	19
4	Terry Jones, MD	20	15	20	20
5	Steven Kempers, MD	52	45	51	52
6	William Ko, MD	12	10	10	12
7	Debra Liu, MD	32	27	32	32
8	Robert Matheson , MD	48	44	48	48
9	Jeffrey Moore, MD	117	97	117	117
10	Shari Skinner, MD	60	48	60	60
11	James Solomon, MD	17	15	17	17
12	Dow Stough, MD	42	38	42	42
13	Leonard Swinyer, MD	34	30	34	34
14	Hector Wiltz, MD	32	26	31	32
15	Craig Leonardi, MD	4	2	4	4
16	Suzanne Bruce, MD	19	18	19	19
Total		564	471	558	564

[1]Evaluated for Efficacy
[2]Evaluated for Safety

Study Period: November 16, 2005 to August 1, 2006

Enrollment: A total of five hundred sixty four (564) patients were randomized into the study.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 78-548, Vol. 1.1-1.6, electronic data submitted on 10/16/06

Study Amendment: On March 19, 2008, the OGD asked the sponsor to provide additional data including sample case report forms. In response, the sponsor submitted data in the study amendment dated March 31, 2008.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

A DSI inspection was not requested for this study due to an acceptable inspection history for two of the same clinical sites (#4, 10). See Section VI A below for details.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor's original protocol and patient consent form were approved on November 9, 2005 by the central Investigational Review Board (IRB), (b) (4) (b) (4) The amended protocol and revised patient consent form were approved on December 2, 2005. The revised consent form changed only the number of subjects who were to participate in the study from 476 to 553.

Reviewer's Comment: *The sponsor's study appears to be in compliance with accepted ethical standards.*

D. Evaluation of Financial Disclosure

The sponsor declared that they have not entered into any financial arrangement with the clinical investigators where the value of compensation of the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a).

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The FDA analysis confirms bioequivalence of the test and the reference products.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #ALT 0432-01-01) was reviewed to evaluate the bioequivalence of the test product and the reference product. The primary endpoint of this study is the complete clearance of AK lesions (zero clinically visible actinic keratosis lesions in the treatment area) at 8-week post-treatment (week 24). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. The sponsor's protocol (P04-034) was reviewed by the OGD prior to the ANDA submission.

2. Two amendments were applied to the original protocol ALT 0432-01-01 (October 14, 2005). Amendment #1 dated October 31, 2005 modified the definition of "female of childbearing potential", increased the number of sites for participation in the study, and removed the requirement for recording the day and time of study medication removal. The amended protocol required that patients remove study medication within 6-10 hours after application.
3. Amendment #2 dated November 4, 2005 increased the total number of patients for enrollment in order to have a sufficient number of patients in the per protocol population. The definition for severity of local skin reaction was also corrected. The study was initiated after approval of Amendment #2.
4. The original patient Informed Consent Form (version dated 11/4/05) was approved by the IRB on 11/9/05 and was revised on 12/2/05 after initiation of the study. The revised informed consent form (version dated 12/2/05) only changed the number of subjects who were to participate in the study from 476 to 553.

Protocol Review (ALT 0432-01-01):
Title: A Multi-Center, Double-Blind, Randomized, Vehicle Controlled, Parallel Group Study Comparing NYCOMED US Inc.'s (formerly Altana, Inc.) Imiquimod Cream 5% to Aldara® (imiquimod) Cream, 5% and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis.

Objective: The purpose of this study was to compare the safety and efficacy profiles of Nycomed's Imiquimod Cream, 5% to Graceway Pharmaceuticals' Aldara® Cream, 5%, and to demonstrate the superior efficacy of the two active creams over that of Nycomed's vehicle (placebo) in the treatment of Actinic Keratosis.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group study design comparing the following three products:

1. Test: Imiquimod Cream, 5%, Nycomed US Inc., lot #T045, manufactured on 6/29/05
2. Reference: Aldara® Cream (imiquimod cream, 5%), Graceway Pharmaceuticals, lot #FG036A, expiration dated 7/06
3. Placebo (Vehicle): Nycomed US Inc., lot#T052

Patients were instructed to apply the assigned study medication prior to normal sleeping hours two times a week for 16 weeks. With each application, the cream was to be left on the skin for 6-10 hours. After at least 6 hours, but no more than 10 hours, patients were instructed to wash the application area with mild soap and water.

Randomization:
The study medications were assigned to patients in a 3:3:1 ratio. Each number corresponded to a computer-generated randomized treatment group and medication kit.

Blinding:
The study medications in packets were completely covered with white vinyl material. The study patients, investigators, staff at the study centers, study monitors and data management personnel were blinded to the patient assignment.

Each kit carried a two-part label as well as a blank space for entering the patient's initials and the name of the sponsor. The fixed portion included the study protocol number, patient number, directions for use and storage, an investigational use statement, warning statements, and the sponsor's name. The tear-off portion of each kit label carried the identity of the medication contained in the kit. If the investigator needed to know which medication the patient was receiving in order to make decisions regarding medical management, the covering of the occluded layer of the tear-off label could be scratched off.

All study medications were supplied in single-use packets containing 250 mg of cream. Each patient's treatment unit consisted of 1 box containing 32 packets of study medication.

Study Population:
Patients who met the following criteria were eligible for the study:

Inclusion Criteria
1. Patients with four to ten definite, visible, discrete, nonhyperkeratotic, nonhypertrophic, clinically diagnosed AK lesions located within a contiguous 25-cm^2 treatment area on the face or balding scalp.
2. Male or female at least 18 years of age.
3. Women of childbearing potential (not postmenopausal for greater than 2 years and have not had a hysterectomy), in addition to having a negative urine pregnancy test, must be willing to use a form of birth control during the study. For the purpose of this study, the following were considered acceptable methods of birth control: oral contraceptives, Norplant®, Depo-Provera®, double barrier methods (e.g., condom and spermicide), IUD, or abstinence with a documented second acceptable method of birth control should the patient become sexually active.
4. Provided IRB approved written informed consent.
5. Patients able to understand and comply with the requirements of the study and be able to complete the study.
6. In good health, as confirmed by medical history and physical exam, and free from any clinically significant disease/condition, other than actinic keratosis, that could have interfered with study evaluations.

Exclusion Criteria
1. Pregnant, nursing, or planning a pregnancy within the study participation period.
2. Known or suspected history of any condition that may be exacerbated by treatment with imiquimod cream 5% or that would impair the examination of the treatment area.
3. Known or suspected history of a clinically significant systemic disease (e.g., immunological deficiencies), unstable medical disorders (e.g., unstable diabetes), life-threatening disease or current malignancies.
4. Immunosuppressed or HIV positive.
5. Known hypersensitivity to any of the following (in any dosage form): imiquimod or any component of the study medications.
6. Received previous treatment with imiquimod cream 5% in the same treatment area.
7. Received radiation therapy and/or anti-neoplastic agents within 3 months prior to study entry.

8. Treated with any of the following therapies within 5 months prior to study entry; psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, or chemical peel.
9. Treated with immunosuppressive medication or oral retinoids (etretinate, Tegison®, Accutane®, cyclosporine) for any indication within 8 weeks prior to study entry.
10. Received any of the following within 4 weeks prior to study enrollment: prescribed topical retinoids (Retin-A®, Differin®, etc.), 5-fluorouracil (Efudex®), masoprocol (Actinex®), cryodestruction, chemodestruction, surgical excision, CO_2 laser vaporization, electrocautery, photodynamic therapy, curettage, interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, systemic corticosteroids, or topical steroids anywhere on the head.
11. Treated with any topical medications (e.g., alpha-hydroxyacids, trichloric acid, glycolic acid, lactic acid) to the face or scalp within 2 weeks prior to study entry.
12. Skin within the treatment area is not healed from previous treatments.
13. Consume excessive amounts of alcohol, abuse drugs, or have any condition that would, in the investigator's opinion, compromise compliance with this protocol.
14. Treated with an investigational drug or investigational device within a period of 30 days prior to study entry.
15. Previously enrolled in this study.

Patients were discontinued from the study for any of the following reasons:

1. Patient's voluntary decision to leave the study for any reason.
2. Investigator’s decision to withdraw patients in the event of intercurrent illness, adverse events, protocol violation, or other reasons.
3. Patient withdrew his or her consent for any reason.
4. Patient's condition worsened to a degree that the investigator felt it was unsafe for the patient to continue in the study.
5. Patient desired to discontinue treatment due to an adverse event.
6. Had a significant protocol violation.
7. Concomitant therapy was reported or required which was liable to interfere with the results of the study.
8. Patient had missed more than 6 consecutive study medication applications.
9. Lost to follow-up.
10. Patient became pregnant.
11. Other administrative reasons.

Patients were instructed to take the following precautions during the study:

1. Wash hands before and after applications.
2. Not to allow the study medication to come in contact with their eyes, mouth, lips, or nostrils.
3. Avoid excessive exposure to the sun.
4. Minimize or avoid exposure to natural sunlight.
5. Not to apply any other treatments (other creams, moisturizers, etc.) to the affected skin for the entire study period. Sunscreen use was permitted while the study medication was not on the skin.

The following medications and procedures were prohibited during the study:

1. Any therapy for actinic keratoses:

- Prescription topical retinoids (Retin-A®, Differin®, etc), 5-fluorouracil (Efudex®), masoprocol (Actinex®), cryodestruction, chemodestruction, surgical excision, CO_2 laser vaporization, electrocautery, photodynamic therapy, curettage, interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, systemic corticosteroids, or topical steroids anywhere on the head.
- Prescription and OTC medications, such as podophyllin, colchicines, bichloracetic acid, trichloroacetic acid, cantharidin, topical salicylic acid, diclofenac sodium (Solaraze®), etc.

2. Microderm abrasion.
3. Moisturizers, over-the-counter retinol products, or products containing α- or β-hydroxyl acids in the treatment area.
4. Immunosuppressive medications for any indication.
5. Tanning booths or nonprescription UV light sources.

Procedures/Observations, and safety measures:

The following procedures were scheduled in this study:

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5/ End of Therapy	Visit 6/ End of Study	Unscheduled Visit
Visit Day	Day 1 (Baseline)	Day 14 (± 4) Week 2	Day 28 (± 7) Week 4	Day 56 (± 7) Week 8	Day 112 (± 7) Week 16	Day 168 (± 7) Week 24	
Screening/Consent	X						
Demographics	X						
Medical History	X						
Physical Exam (including vital signs)	X						
Urine Pregnancy Test *	X						
Inclusion/Exclusion Criteria Review	X						
Assessment of Diagnosis of Actinic Keratosis	X						
Actinic Keratosis Counts	X	X	X	X	X	X	X
Local Skin Reactions/ Irritation	X	X	X	X	X	X	X
Adverse Event Reporting		X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Drug Dispensing	X	X	X	X	X		
Subject Instruction/ Compliance Review	X	X	X	X	X	X	X
Drug Return, Accountability		X	X	X	X	X	If applicable

* For females of child-bearing potential – to be completed in doctor's office prior to enrollment.

1. Patients who met the entry criteria were examined to confirm the definite clinical diagnosis of 4-10 AK lesions located within a contiguous 25-cm^2 treatment area (e.g., 5 cm X 5 cm or 3 cm X 8.3 cm or 2 cm X 12.5 cm) on the face or balding scalp.
2. The AK lesions were recorded descriptively on the anatomical diagram in the patient's source document.

3. All AK lesions within the treatment area were considered the baseline/target actinic keratoses. The patient's Fitzpatrick Skin Type was assessed and recorded at baseline.
4. The same investigator, to the extent possible, identified, counted, and located the target/baseline AK lesions.
5. Patients were instructed to apply the study medication only to the targeted area. The cream was applied 2 times a week prior to normal sleeping hours for 16 weeks. Examples of two times a week applications were scheduled on Monday and Thursday, or Tuesday and Friday. If a patient forgot to apply the cream, the missed dose of cream was to be applied the next day prior to sleeping hours and then continue on the regular scheduled day. Patients were instructed to use a new foil pack of cream for each application and no more than one foil pack for each application.
6. The local skin reactions were evaluated for intensity at each visit using the following four-point scale (0-3):

   Erythema: redness
   0=none; no visible pink or red
   1=mild; faint pink tone
   2=moderate; pink to red tone
   3=severe; definite distinct red tone

   Scabbing/crusting: a crust formed and covered a healing lesion
   0=none; no scabs or crusts
   1=mild; few small areas of scabbing/crusting seen on close exam
   2=moderate; larger areas of scabbing/crusting; easily noticeable
   3=severe; widespread areas of scabbing/crusting noticed at first glance

   Flaking/scaling/dryness: dry, thin flakes, or sheets of epidermis shedding from the Skin
   0=none; no flaking/scaling/dryness
   1=mild; slight flaking/scaling/dryness seen on close exam only
   2=moderate; distinct flaking/scaling/dryness; easily noticeable
   3=severe; marked/intense heavy flaking/scaling/dryness notices at first glance

   Erosion/ulceration: destroyed skin surface; lesion with pus and necrosis of surrounding tissue
   0=none; no erosion/ulceration
   1=mild; small superficial erosion/ulceration seen only on close exam
   2=moderate; more prominent, distinct erosion/ulceration easily noticeable
   3=severe; marked/intense, widespread erosion/ulceration noticed at first glance

7. The following window conventions were scheduled by the sponsor for the clinical evaluations and local skin reactions:

Visit	Target day	window
2	14	Between days 10 and 18
3	28	Between days 21 and 35
4	56	Between days 49 and 63
5	112	Between days 105 and 119
6	168	Between days 161 and 175

Treatment Compliance:
Patients who missed more than 6 consecutive applications were considered non-compliant by the sponsor and were discontinued from the study.

Endpoints:
The primary endpoint of this study evaluated by the sponsor was complete clearance of the actinic keratoses in the treatment area. Complete clearance was defined by the sponsor as a post treatment count of zero (0) clinically visible AK lesions in the treatment area. The primary analyses were performed for the visit 6/week 24 (8 weeks follow-up) results in the MITT and PP populations.

The test of superiority was based on the difference between each active treatment's success (complete clearance of AK in the treatment area) rate compared with that of the vehicle at visit 6/week 24.

The sponsor evaluated the proportion of patients who achieved complete or partial clearance of AK lesions in the treatment area as a secondary endpoint. Partial clearance was defined as having a 75% or greater reduction in the clinically visible AK lesions in the treatment area compared to baseline. Secondary efficacy outcomes were evaluated at visit 6/week 24 (8 weeks follow-up) for both the MITT and PP populations.

Reviewer's Comment: *The sponsor's proposed secondary endpoints were considered supportive information.*

Statistical analysis plan
Primary Endpoint: The primary endpoint of this study was complete clearance of AK lesions in the treatment area.

Sample Size: The sample size of 553 patients (237:237: 79; test: reference: vehicle) was determined based on the sponsor's estimation of success (complete clearance of AK lesions) rate of 50% for both the test and reference products and no greater than 15% for the vehicle. The sponsor estimated that this sample size would provide at least a 0.90 probability of showing bioequivalence of the test and reference products (90% CI criteria) in the PP population and demonstrate superiority of the active treatments over the vehicle ($p<0.05$) in the MITT population, using independent, continuity-corrected Z-tests.

Analysis: For the bioequivalence analysis, the 90% confidence interval was constructed for the difference in the proportion of patients with complete clearance of AK lesions between the test product and reference product at Visit 6/week 24 (8 weeks follow-up). The confidence interval was calculated using Wald's method with Yates' continuity correction based on the data pooled from all clinical sites . Bioequivalence was established if this 90% confidence interval was contained within the interval of (–0.20 to +0.20). The analysis in the PP population was considered primary and that in the MITT population as supportive information.

According to the sponsor, the MITT population was the primary population for comparison of the difference in proportion of patients with complete clearance of AK between the active treatment groups and the vehicle group.

The incidence of all adverse events, tabulated for each treatment group, was summarized by the sponsor using MedDRA dictionary. The safety of the test and reference products was demonstrated primarily by descriptive statistical summaries of their adverse event profiles (frequency and intensity of events). Local skin reactions of erythema, scabbing/crusting, flaking/scaling/dryness and erosion/ulceration were summarized by treatment group, frequency, and severity. Statistical significance between active treatment groups were evaluated by the sponsor using Cochran-Mantel-Haenszel test for raw mean scores, adjusted for site. The safety analyses were conducted on the Intent-to-Treat population only.

Any patient who terminated the study prematurely due to insufficient therapeutic response (condition worsened) after at least 14 days of treatment with a compliance rate of at least 80% and no significant protocol violations was carried forward as a treatment failure in both PP and MITT population analyses if the patient met all other criteria for inclusion in those populations.

Study Conduct
Discussion of ITT and PP populations:

Three patient populations were defined by the sponsor as follows:
intent-to-treat (ITT)
a. enrolled into the study
b. received at least one application of study treatment
modified intent-to-treat (MITT)
a. enrolled into the study
b. had 4-10 definite, visible, discrete, nonhyperkeratotic, nonhypertrophic, clinically diagnosed AK lesions located within a contiguous 25-cm^2 treatment area on the face or balding scalp
c. received at least one application of study medication
d. had at least one post-baseline efficacy evaluation
per-protocol (PP)
a. enrolled into the study
b. met inclusion/exclusion criteria
c. took between 70% -120% of expected study medication applications.
d. had not taken any concomitant medications prohibited by the protocol and had no other significant protocol violations
e. did not miss greater than 6 consecutive study medication applications AND returned for visit 6/end of study within the visit windows and had data on the primary efficacy variables for all clinical evaluations, OR met per protocol criteria up to the time of early study discontinuation due to treatment failure after applying study medication for at least 12 weeks (with a compliance rate of 70%).

Retention of Reserve Samples:
The sponsor stated that each investigational site randomly selected and kept the retention samples at their facility (one block of study medication which equals 7 consecutively numbered patient kits of study medication) in accordance with 21 CFR 320.63 and 320.38.

Demographics and Baseline AK lesion count:
A total of 564 patients, four hundred sixty seven (467) males and ninety seven (97) females, were enrolled into the study. Of these, 513 completed the study and 51 discontinued. All patients were defined by the sponsor as White and no other race was included in this study. Baseline demographics, age, and race in the ITT population were similar in all treatment groups. The mean age was 66.5 years (35-93), 66.5 (40-86), and 67.1 (41-85) in the test, reference, and vehicle groups, respectively. The mean AK lesion counts at baseline for the ITT population were not statistically significant in all treatment groups. The demographic characteristics for all enrolled patients are tabulated by the sponsor in Table I.

Table I: Demographic Characteristics for Intent-to-Treat Patients (per sponsor)

Parameter	Category	Reference (N=242)	Test (N=240)	Vehicle (N=82)	Overall (N=564)	p-value[3]
Gender (n,%)	Male	197 (81.4%)	198 (82.5%)	72 (87.8%)	467 (82.8%)	0.396[1]
	Female	45 (18.6%)	42 (17.5%)	10 (12.2%)	97 (17.2%)	
Ethnicity (n,%)	Hispanic or Latino	11 (4.5%)	14 (5.8%)	1 (1.2%)	26 (4.6%)	0.078[1]
	Not Hispanic or Latino	231 (95.5%)	226 (94.2%)	81 (98.8%)	538 (95.4%)	
Race (n,%)	White	242 (100.0%)	240 (100.0%)	82 (100.0%)	564 (100.0%)	NA
	Black or African-American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	1 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)	
Age (years)	Mean ± SD	66.5 ± 10.13	66.5 ± 10.10	67.1 ± 10.27	66.6 ± 10.12	0.900[2]
	Min - Max	40 - 86	35 - 93	41 - 85	35 - 93	
Height (inches)	Mean ± SD	68.6 ± 3.88	68.4 ± 3.57	68.6 ± 3.21	68.5 ± 3.65	0.466[2]
	Min - Max	55.3 - 78.0	55.0 - 76.0	59.0 - 74.0	55.0 - 78.0	
Weight (lbs)	Mean ± SD	188.3 ± 34.99	185.8 ± 34.38	182.9 ± 28.27	186.4 ± 33.82	0.962[2]
	Min - Max	124.0 - 350.0	105.0 - 300.0	100.0 - 252.0	100.0 - 350.0	
Total Number of AK Lesion	Mean ± SD	5.74 ± 1.710	5.70 ± 1.618	5.74 ± 1.811	5.72 ± 1.684	0.725[2]
	Min - Max	4 - 12	4 - 10	4 - 11	4 - 12	

Note: Bi-racial or multi-racial subjects are counted more than once in the summary of race
[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-values for treatment comparisons from Friedman's test with factors of treatment and site.
[3] P-values are given for equality comparisons between the three dosing groups.

Local Skin Reaction at baseline

According to the sponsor's analysis, local skin assessments observed at baseline for the ITT population were similar in all treatment groups and were not statistically significant. The majority of patients at baseline did not have any erosion or ulceration. Most patients had comparable erythema (mild to moderate) and flaking/scaling/dryness (mild to moderate) in all treatment groups. More patients in the test group reported severe erythema at baseline compared to the reference group (4.2% T vs. 2.1% R) as shown in Table II.

Table II. Local Skin Reactions at Baseline (per sponsor)

Parameter	Category	Reference (N=242)	Test (N=240)	Vehicle (N=82)	p-value Reference vs. Test
Erythema	None	48 (19.8%)	54 (22.5%)	19 (23.2%)	0.723[1]
	Mild	128 (52.9%)	123 (51.3%)	30 (36.6%)	
	Moderate	61 (25.2%)	53 (22.1%)	30 (36.6%)	
	Severe	5 (2.1%)	10 (4.2%)	3 (3.7%)	
Scabbing/Crusting	None	170 (70.2%)	173 (72.1%)	57 (69.5%)	0.239[1]
	Mild	41 (16.9%)	38 (15.8%)	17 (20.7%)	
	Moderate	29 (12.0%)	29 (12.1%)	7 (8.5%)	
	Severe	2 (0.8%)	0 (0%)	1 (1.2%)	
Flaking/Scaling/Dryness	None	47 (19.4%)	44 (18.3%)	11 (13.4%)	0.986[1]
	Mild	133 (55.0%)	137 (57.1%)	47 (57.3%)	
	Moderate	57 (23.6%)	53 (22.1%)	22 (26.8%)	
	Severe	5 (2.1%)	6 (2.5%)	2 (2.4%)	
Erosion/Ulceration	None	227 (93.8%)	227 (94.6%)	76 (92.7%)	0.644[1]
	Mild	13 (5.4%)	12 (5.0%)	6 (7.3%)	
	Moderate	2 (0.8%)	1 (0.4%)	0 (0%)	
	Severe	0 (0%)	0 (0%)	0 (0%)	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

Efficacy Results

Five hundred sixty-four (564) patients were randomized to receive the study treatment; 240 in the test, 242 in the reference, and 82 in the vehicle group. The most common reason for discontinuation from the study was due to withdrawal of consent. Three patients in the test group and one in the reference group had to be discontinued due to a need for concomitant therapy. Overall, more patients had to be discontinued from the reference group (reference: 11%, test: 9%, vehicle: 4%) compared to the test or vehicle group. The sponsor's disposition of patients is shown in Table III and the reason for discontinuation is listed in Table IV. Tables V and VI show the summary of the sponsor's primary and secondary efficacy outcome analyses.

The original protocol required patients to have 4-10 AK lesions to be considered eligible for enrollment. However, patients enrolled with >10 but less and equal to 12 AK lesions were not excluded from the MITT and PP population by the sponsor. The sponsor stated that 1 or 2 additional lesions would not have had a great impact on the patient's overall severity assessment or result.

Reviewer's Comments: *The sponsor included three patients [(12) #290, #611, #288] who had a baseline AK lesion count greater than 10 in the PP population. Two patients [(12)290 and 611] in the reference group had an AK lesion count of 12 and one patient [(12)288] in the vehicle*

group had an AK lesion count of 11 at baseline. None from the test group had AK lesion counts greater than 10 at baseline. According to the sponsor's inclusion criteria, patients with baseline AK lesion counts of 4-10 were to be enrolled into this study. However, the investigator made the decision not to exclude these patients from the MITT and PP analyses. The investigator believed that having 1 or 2 additional lesions would not have a great impact on the patient's overall severity assessment or result, especially when they were enrolled with >10 but ≤ 12 AK lesions prior to database lock and unblinding. Two of these patients had a decrease in AK lesion count and one patient [(12) 611] had zero AK lesions at the end of study visit. This reviewer agrees with the sponsor that this protocol deviation is not considered likely to affect the outcome of the study.

A pilot study (IND#49, 480, 2/28/01) and #1428-IMIQ study submitted for evaluation of the efficacy of the RLD included patients with baseline AK lesion counts of 9-20 and 6-15, respectively.

Table III. Disposition of Patients (per Sponsor)

	Number (%) of Subjects		
	Reference	**Test**	**Vehicle**
Subjects Randomized	242	240	82
Subjects Excluded from Intent-to-Treat Analysis	0 (0%)	0 (0%)	0 (0%)
Subjects Included in Intent-to-Treat Analysis	242 (100%)	240 (100%)	82 (100%)
Subjects Excluded from Modified Intent-to-Treat Analysis	3 (1%)	2 (1%)	1 (1%)
Subjects Included in Modified Intent-to-Treat Analysis	239 (99%)	238 (99%)	81 (99%)
Subjects Excluded from Per-Protocol Analysis	44 (18%)	39 (16%)	10 (12%)
Subjects Included in Per-Protocol Analysis	198 (82%)	201 (84%)	72 (88%)

Table IV. Patient Discontinuation by Reason (per Sponsor)

	Number (%) of Subjects		
	Reference	**Test**	**Vehicle**
Number Randomized	242	240	82
Number Completed Study[1]	215 (89%)	219 (91%)	79 (96%)
Total Discontinued	27 (11%)	21 (9%)	3 (4%)
Reason Discontinued			
Subject Decision/Withdrew Consent	10 (4%)	11 (5%)	2 (2%)
Subject's Condition Worsened, Investigator Felt It Unsafe for the Subject to Continue[1]	0 (0%)	1 (0%)	0 (0%)
Subject's Study Drug was Unblinded	0 (0%)	0 (0%)	0 (0%)
Adverse Event	6 (2%)	3 (1%)	0 (0%)
Significant Protocol Violation	7 (3%)	1 (0%)	1 (1%)
Concomitant Therapy Reported/Required	1 (0%)	3 (1%)	0 (0%)
Subject Lost to Follow-Up	1 (0%)	0 (0%)	0 (0%)
Subject Missed more than 6 Consecutive Study Medication Applications	0 (0%)	1 (0%)	0 (0%)
Subject Became Pregnant	0 (0%)	0 (0%)	0 (0%)
Administrative Reasons	0 (0%)	0 (0%)	0 (0%)
Other	2 (1%)	1 (0%)	0 (0%)

[1]Subjects who discontinued early due to 'Condition Worsened' were not included in the 'number completed study', but were included in the per-protocol population if they met all other criteria for inclusion in the per-protocol population.

Table V. Primary Efficacy Analysis: Complete Clearance of AK lesions at visit 6/week 24 (8 weeks follow-up); per sponsor

					p-values	
Parameter	**Reference**	**Test**	**Vehicle**	**90% C.I. for Bioequivalence of Test to Reference**	**Reference vs. Vehicle**	**Test vs. Vehicle**
Per-Protocol Subjects (n,%)						
	(N=198)	(N=201)	(N=72)			
Complete Clearance	85 (42.9%)	85 (42.3%)	15 (20.8%)	-8.00% to 9.29%	0.001[2]	0.002[2]
Failure	113 (57.1%)	116 (57.7%)	57 (79.2%)			
Modified Intent-to-Treat Subjects (n,%)						
	(N=239)	(N=238)	(N=81)			
Complete Clearance	101 (42.3%)	95 (39.9%)	15 (18.5%)	-5.48% to 10.17%	<0.001[2]	<0.001[2]
Failure	138 (57.7%)	143 (60.1%)	66 (81.5%)			

Note: Missing efficacy results were replaced using an LOCF approach for mITT subjects who were discontinued early due to treatment failure.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.
[2] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Table VI. Secondary Efficacy Analysis (per Sponsor)

					p-values	
Parameter	**Reference**	**Test**	**Vehicle**	**90% C.I. for Bioequivalence of Test to Reference**	**Reference vs. Vehicle**	**Test vs. Vehicle**
Per-Protocol Subjects (n,%)						
	(N=198)	(N=201)	(N= 72)			
Complete/Partial Clearance	109 (55.1%)	101 (50.2%)	20 (27.8%)	-3.91% to 13.52%	<0.001[2]	0.002[2]
Failure	89 (44.9%)	100 (49.8%)	52 (72.2%)			
Modified Intent-to-Treat Subjects (n,%)						
	(N=239)	(N=238)	(N= 81)			
Complete/Partial Clearance	126 (52.7%)	117 (49.2%)	21 (25.9%)	-4.38% to 11.50%	<0.001[2]	<0.001[2]
Failure	113 (47.3%)	121 (50.8%)	60 (74.1%)			

Note: Missing efficacy results were replaced using a LOCF approach for mITT subjects who were discontinued early due to treatment failure.
[1] Confidence interval calculated using Wald's method with Yates' continuity correction.
[2] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Reviewer's Comments: *For the FDA statistical analysis, the following adjustments to the MITT and PP populations were requested:*

Site/#	*Treatment*	*Reason for inclusion/exclusion by the sponsor*	*Comments*
2/342	*Reference*	*Excluded from the PP population analysis due to violation of exclusion criterion #10.*	*Should also be excluded from the MITT population due to violation of exclusion criterion.*
2/696	*Reference*	*Patient discontinued from the study due to worsening of AK.*	*Due to treatment failure, this patient should be included in the PP population as a treatment failure.*
8/404	*Reference*	*Excluded from the PP population analysis due to violation of exclusion criterion #11; applied Metrogel on the face for treatment of rosacea prior to visit and ongoing.*	*Should also be excluded from the MITT population.*
10/469	*Reference*	*Patient was excluded from the PP population due to violation of exclusion criterion #3 (do not qualify).*	*In the case report form, the sponsor documented that this patient had BCC at baseline and violated exclusion criterion #3. Due to violation of exclusion criterion, this patient should also be excluded from the MITT population.*
10/476	*Reference*	*Patient was excluded from the PP population due to violation of exclusion criterion #3, and patient became unblinded by peeling off the study drug label.*	*In the case report form, the sponsor documented that this patient had BCC removed 2 weeks before the study entry and violated exclusion criterion #3. Due to violation of exclusion criterion, this patient should also be excluded from the MITT population.*
10/504	*Reference*	*Patient was excluded from the PP population due to violation of exclusion criterion #14-participation in* (b) (6) *investigational study.*	*Should also be excluded from the MITT population.*
11/254	*Reference*	*Patient was excluded from the PP population due to violation of exclusion criterion #6-significant disease that may interfere with study evaluation.*	*In the case report form, the sponsor documented that this patient did not meet inclusion criterion #6 but was included in the study marked with "yes". This patient also had rosacea on the face. Due to violation of inclusion criterion, this patient should also be excluded from the PP population.*
12/294	*Reference*	*Patient was excluded from the PP population due to violation of exclusion criterion #10-received systemic steroids within 4 weeks prior to study entry.*	*Should also be excluded from the MITT population.*
16/745	*Reference*	*Patient was treated with topical corticosteroid for treatment of seborrheic dermatitis during the study.*	*In the case report form, the sponsor documented that the topical corticosteroid was not applied to the target lesion (forehead). Topical corticosteroid was applied to scalp only. No patient adjustment is needed.*

Site/#	*Treatment*	*Reason for inclusion/exclusion by the sponsor*	*Comments*
2/365	*Test*	*Patient was excluded from the PP population due to violation of exclusion criterion #10-received systemic steroid within 4 weeks prior to study entry.*	*Should also be excluded from the MITT population.*
8/386	*Test*	*Patient was excluded from the PP population due to violation of exclusion criterion #10-received systemic steroid within 4 weeks prior to study entry.*	*Should also be excluded from the MITT population.*
9/47	*Test*	*Patient was treated with topical corticosteroid for irritant dermatitis during the study.*	*The sponsor commented that the topical corticosteroid was applied on the back, legs and arms for irritant dermatitis. Since it was not applied at the treatment site, no patient adjustment is needed.*
9/659	*Test*	*Patient was discontinued due to worsened condition.*	*Should be included in the PP population as a treatment failure.*
10/527	*Test*	*Patient was excluded from the PP population due to violation of exclusion criterion (#3).*	*In the case report form, the sponsor documented that BCC was diagnosed on the patient's neck at visits 2-3. The sponsor excluded this patient from the PP population because it was considered as a violation of exclusion criterion #3. Since the patient was not diagnosed with BCC at baseline and the BCC was not present at the treatment site (forehead), this patient is not considered to have violated exclusion criterion #3 and may be included in the MITT population as already done by the sponsor. Since it is not considered a violation of exclusion criterion, this patient needs to be included in the PP population.*
12/616	*test*	*Patient was excluded from the PP population due to violation of exclusion criterion #10-received systemic steroid within 4 weeks prior to study entry.*	*Should also be excluded from the MITT population.*
10/468	*Vehicle*	*Patient was excluded from the PP population due to violation of exclusion criterion #3-basal cell carcinoma present*	*Should also be excluded from the MITT population.*

- *Only two patients [(2) 362, (8) 404)] less than 75% dosing compliance were included in the sponsor's PP population. These two patients took 23 doses (72%), one dose less than the usual recommended minimum compliance of 75% (24 doses). The maximum treatment compliance in the sponsor's PP population was 115%, within the sponsor's specified upper limit of 120%. Although treatment compliance of 75%-125% is generally recommended to be included in the PP population analysis, this sponsor's defined compliance of 70%-120% is acceptable for this study.*

D. Bioequivalence Conclusion

Based on the FDA statistical analyses, the study in the treatment of AK demonstrates that the 90% CI of the difference in success (complete clearance of AK lesions) rate between the test and the reference products at visit 6/week 24 (8 weeks follow-up) in the PP population is (-0.094, 0.078), which is within the bioequivalence limits of (-0.20 to +0.20). Both the test and reference products also demonstrate superiority over the vehicle ($p<0.001$) at visit 6 in the MITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between the products.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

The study showed no meaningful difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

The overall incidence of adverse events by severity was similar in both active treatment groups. A total of 224 patients (94 in the test, 104 in the reference, and 26 in the vehicle group) experienced one or more treatment-emergent adverse events and 9 patients discontinued the study due to an adverse event. Twenty-five (25) patients had at least one adverse event that was considered to be severe; 9 in the test, 14 in the reference and 2 in the vehicle group. Of these patients, only one event (application site reaction/application site infection) in the reference group was considered probably related to the study drug. The most frequent adverse event reported in the study was infections/infestations (17.5% in the reference, 18.6% in the reference, and 13.4% in the vehicle group). Except for one patient in the reference group (application site infection), they were considered not related to the study drugs.

Skin-related adverse events regardless of relationship to the study medication occurred in 24 (10%) patients in the test group, 29 (12%) in the reference group, and 5 (6.1%) in the vehicle group. Skin-related adverse events probably or definitely related to the study medication occurred in 5 patients (2.1%) in the test group, 6 (2.5%) in the reference group, and none in the vehicle group. According to the sponsor's analysis, the difference between the test and reference group with regard to the occurrence of skin-related adverse events was not statistically significant ($p\geq 0.488$).

No deaths occurred in the study. Fifteen serious adverse events were experienced by 13 patients (7 test, 6 reference) but were judged by the sponsor to be unrelated to the study medication.

The sponsor's summary of adverse events is listed in Tables VII and VIII below. The list of serious adverse events by patient is shown in Table IX.

Reviewer's Comment: *The frequency of adverse events related to the study treatment was comparable between the test and reference groups.*

Table VII. Treatment-Emergent Adverse Events by Relationship (per sponsor)

Type	Parameter	Reference (N=242)	Test (N=240)	Vehicle (N=82)	p-value Reference vs. Test
Overall	Subjects with Adverse Event(s) Regardless of Relationship to Study Medication	104 (43.0%)	94 (39.2%)	26 (31.7%)	0.379[1]
	Subjects with Adverse Event(s) Probably Related or Definitely Related to Study Medication	6 (2.5%)	7 (2.9%)	0 (0%)	0.754[1]
Skin Related	Subjects with Adverse Event(s) Regardless of Relationship to Study Medication	29 (12.0%)	24 (10.0%)	5 (6.1%)	0.488[1]
	Subjects with Adverse Event(s) Probably Related or Definitely Related to Study Medication	6 (2.5%)	5 (2.1%)	0 (0%)	0.781[1]

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.

Table VIII. Serious Adverse Events (per sponsor)

Body System	Preferred Term	Number (%) of Subjects		
		Reference (N=242)	Test (N=240)	Vehicle (N82)
Subjects with at Least One SAE		6 (2.53%)	7 (2.9%)	0 (0%)
CARDIAC DISORDERS	Body System Total	0 (0%)	1 (0.4%)	0 (0%)
	Coronary Artery Disease	0 (0%)	1(0.4%)	0 (0%)
GASTROINTESTINAL DISORDERS	Body System Total	3 (1.2%)	1(0.4%)	0 (0%)
	Abdominal Pain Upper	1 (0.4%)	1 (0.4%)	0 (0%)
	Haemorrhoids	1 (0.4%)	0 (0%)	0 (0%)
	Large Intestine Perforation	1 (0.4%)	0 (0%)	0 (0%)
GENERAL DISORDERS	Body System Total	1 (0.4%)	0 (0%)	0 (0%)
	Chest Pain	1 (0.4%)	0 (0%)	0 (0%)
INFECTIONS AND INFESTATIONS	Body System Total	1 (0.4%)	2 (0.83%)	0 (0%)
	Arthritis Bacterial	0 (0%)	1 (0.4%)	0 (0%)
	Diverticulitis	1 (0.4%)	0 (0%)	0 (0%)
	Labyrinthitis	0 (0.0%)	1 (0.4%)	0 (0%)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	Body System Total	1 (0.4%)	0 (0%)	0 (0%)
	Road Traffic Accident	1 (0.4%)	0 (0%)	0 (0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER	Body System Total	0 (0.0%)	1 (0.4%)	0 (0%)
	Osteoarthritis	0 (0.0%)	1 (0.4%)	0 (0%)
NERVOUS SYSTEM DISORDER	Body System Total	0 (0.0%)	1 (0.4%)	0 (0%)
	Transient Ischemic Attack	0 (0%)	1 (0.4%)	0 (0%)
REPRODUCTIVE SYSTEM	Body System Total	1 (0.4%)	1 (0.4%)	0 (0%)
	Ovarian Mass	0 (0%)	1 (0.4%)	0 (0%)
	Priapism	1 (0.4%)	0 (0%)	0 (0%)
SURGICAL AND MEDICAL PROCEDURES	Body System Total	1 (0.4%)	0 (0%)	0 (0%)
	Laparoscopic surgery	1 (0.4%)	0 (0%)	0 (0%)

Table IX. Summary of Serious Adverse Events by Patients (per reviewer)

Site/patient number	Treatment	Event
02/0364	Reference	Motor vehicle accident
02/0365	Test	CAD; hospitalized due to coronary artery bypass graft surgery
04/0231	Reference	#1.diverticulitis: Patient was hospitalized due to severe diverticulitis. This patient had been diagnosed 3 months prior to the study with extensive diverticular disease by colonoscopy. #2. perforated colon: shortly after episode of diverticulitis, this patient was hospitalized again and underwent sigmoid colorectomy.
05/0145	Test	Labyrinthitis; Patient was admitted to the hospital due to an adverse event.
05/0711	Test	Septic arthritis of left knee; Patient was admitted to the hospital due to a fall.
05/0723	Test	Severe stomach pain; Patient was admitted to the hospital due to severe stomach pain.
07/0300	Test	Worsening of right knee osteoarthritis; Patient was hospitalized and underwent right knee replacement surgery.
09/0047	Test	Transient Ischemic Attack; Patient was discharged and the event was resolved.
09/0672	Reference	Laparoscopic cholecystectomy; Patient had history of chronic cholecystitis and a cholecystectomy was performed.
10/0465	Reference	Stomach Pain; Patient went to the emergency room due to stomach pain and was discharged with improvement of his condition. Patient had history of diverticulitis.
10/0491	Test	Ovarian Mass; Patient's regular physician visit noted an abdominal mass. The patient underwent a hysterectomy and the ovarian mass was determined to be benign.
11/0252	Reference	Chest pain; Patient was hospitalized for chest pain.
13/0194	Reference	#1. Lower gastrointestinal bleed: Patient was admitted to the hospital due to rectal bleeding secondary to hemorrhoids. Patient had a ruptured artery in the anal area and underwent surgery to repair the artery. #2. Priapism: Patient was hospitalized on (b) (6) after 4 to 7 day history of priapism. After operative procedure, the patient was discharged on (b) (6) (b) (6)

Evaluation of Local Skin Reactions

According to the sponsor's analysis, no significant differences between the two active treatments were observed for local skin reaction at visit 5 and visit 6. Compared to the baseline, more patients reported "none" for each local skin reaction, showing some improvement in severity by visit 6. The frequency and severity of local skin reactions were tabulated by the sponsor in Tables X and XI.

Table X. Evaluation of Local Skin Reaction for Intent to Treat Patients at visit 5 (end of therapy), per sponsor

Parameter	Category	Reference (N=217)	Test (N=221)	Vehicle (N=79)	p-value Reference vs. Test
Erythema	Missing	1 (0.5%)	0 (0%)	0 (0%)	
	None	57 (26.3%)	52 (23.5%)	26 (32.9%)	0.091[1]
	Mild	89 (41.0%)	84 (38.0%)	38 (48.1%)	
	Moderate	55 (25.3%)	60 (27.1%)	12 (15.2%)	
	Severe	15 (6.9%)	25 (11.3%)	3 (3.8%)	
Scabbing/Crusting	Missing	1 (0.5%)	0 (0%)	0 (0%)	
	None	143 (65.9%)	145 (65.6%)	53 (67.1%)	0.605[1]
	Mild	45 (20.7%)	42 (19.0%)	18 (22.8%)	
	Moderate	20 (9.2%)	27 (12.2%)	6 (7.6%)	
	Severe	8 (3.7%)	7 (3.2%)	2 (2.5%)	
Flaking/Scaling/Dryness	Missing	1 (0.5%)	0 (0%)	0 (0%)	
	None	82 (37.8%)	78 (35.3%)	28 (35.4%)	0.306[1]
	Mild	100 (46.1%)	101 (45.7%)	40 (50.6%)	
	Moderate	27 (12.4%)	33 (14.9%)	8 (10.1%)	
	Severe	7 (3.2%)	9 (4.1%)	3 (3.8%)	
Erosion/Ulceration	Missing	1 (0.5%)	0 (0%)	0 (0%)	
	None	203 (93.5%)	201 (91.0%)	78 (98.7%)	0.218[1]
	Mild	9 (4.1%)	14 (6.3%)	1 (1.3%)	
	Moderate	4 (1.8%)	5 (2.3%)	0 (0%)	
	Severe	0 (0%)	1 (0.5%)	0 (0%)	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

Table XI. Evaluation of Local Skin Reaction for Intent to Treat Patients at visit 6/week 24 (8 weeks follow-up), per sponsor

Parameter	Category	Reference (N=234)	Test (N=236)	Vehicle (N=81)	p-value Reference vs. Test
Erythema	None	126 (53.8%)	121 (51.3%)	28 (34.6%)	0.565[1]
	Mild	87 (37.2%)	90 (38.1%)	39 (48.1%)	
	Moderate	12 (5.1%)	17 (7.2%)	12 (14.8%)	
	Severe	9 (3.8%)	8 (3.4%)	2 (2.5%)	
Scabbing/Crusting	None	205 (87.6%)	200 (84.7%)	57 (70.4%)	0.437[1]
	Mild	15 (6.4%)	18 (7.6%)	16 (19.8%)	
	Moderate	8 (3.4%)	12 (5.1%)	7 (8.6%)	
	Severe	6 (2.6%)	6 (2.5%)	1 (1.2%)	
Flaking/Scaling/Dryness	None	134 (57.3%)	136 (57.6%)	38 (46.9%)	0.883[1]
	Mild	85 (36.3%)	81 (34.3%)	34 (42.0%)	
	Moderate	10 (4.3%)	15 (6.4%)	7 (8.6%)	
	Severe	5 (2.1%)	4 (1.7%)	2 (2.5%)	
Erosion/Ulceration	None	231 (98.7%)	230 (97.5%)	79 (97.5%)	0.285[1]
	Mild	1 (0.4%)	2 (0.8%)	2 (2.5%)	
	Moderate	1 (0.4%)	1 (0.4%)	0 (0%)	
	Severe	1 (0.4%)	3 (1.3%)	0 (0%)	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

Reviewer's Comment: *As expected, a more intense degree of local skin reaction occurred with the active treatments compared to the vehicle. Compared to baseline, more patients had severe erythema, scabbing/crusting, and erosion/ulceration in the active treatment groups.*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report

A DSI inspection was not requested for this study due to an acceptable inspection history from the same clinical sites (#4, 10) and same investigators for other studies (ANDA 76-419, Nycomed's [formerly Altana Inc.] ketoconazole shampoo, and 76-498, Spear Pharmaceuticals' Tretinoin cream).

No FDA Form 483 was issued from the previous DSI inspection of ANDA 76-419 (Dr. Terry Jones) and ANDA 76-498 (Dr. Shari Skinner).

B. Review of the FDA Statistical Report (1/11/09)

The conclusion of the FDA statistical analysis confirms the bioequivalence of the test and the reference products. The 90% CI of the difference in success (complete clearance of AK lesions) rate between the test and the reference products at visit 6 (8 weeks follow-up) is (-0.094, 0.078), which is within the bioequivalence limits of (-.20 to +.20). Both test and the reference products showed superiority over the vehicle group ($p<0.001$) at visit 6.

Based on this reviewer's comments above, 203 patients in the test group, 199 patients in the reference group, and 72 patients in the vehicle group were included in the FDA PP population analysis.

The FDA statistician provided a summary of the patient distributions, equivalence test for the per protocol population and efficacy analyses for the FDA MITT population as follows:

1 - Population distributions

Population	Test (N = 240)	Reference (N = 242)	Vehicle (N = 82)	Total (N = 564)
Subjects In the ITT	240 (100%)	242 (100%)	82 (100%)	564 (100%)
Patients Excluded from MITT	5 (2%)	10 (4%)	2 (2%)	17 (3%)
Total Patients in the MITT	235 (98%)	232 (96%)	80 (98%)	547 (97%)
MITT Patients Excluded from PP	32 (13%)	33 (14%)	8 (10%)	73 (13%)
Total Patients in the PP	203 (85%)	199 (82%)	72 (88%)	474 (84%)

2- Efficacy Analyses

Parameter	MITT Population			p-value [1]	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Complete Clearance Rate at visit 6	40% (94/235)	43% (100/232)	19% (15/80)	< 0.001	< 0.001
Partial Clearance Rate at visit 6	49% (116/235)	54% (125/232)	26% (21/80)	< 0.001	< 0.001

[1] p-values for treatment groups comparisons based on the two-sided Fisher's exact test.

3- Bioequivalence Analyses

Parameter	PP Population			
	Test	Reference	The 90% CI for the Test and Reference	Is the 90% CI within (-20%,20%)?
Complete Clearance Rate at visit 6	42% (85/203)	43% (85/199)	(-9.4 , 7.8)	YES
Partial Clearance Rate at visit 6	50% (102/203)	55% (109/199)	(-13.2 , 4.2)	YES

Reviewer's Comment: *The FDA statistical analysis confirms the bioequivalence of the test and reference products in the PP population. Both the test and reference products demonstrated superiority over the vehicle in the MITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between the products.*

VII. Formulation

Formulation Comparison

		Nycomed US Inc.'s formulation		**Reference***
Ingredient	**Function**	**Amount % w/w**	**Ingredient**	**% (w/w)**
Imiquimod	Active	5.000	Imiquimod	5.0
Oleic acid NF	(b) (4)	(b) (4)	Isostearic acid	(b) (4)
Benzyl alcohol, NF			Benzyl alcohol, USP	
Polysorbate 60, NF			Polysorbate 60, NF	
Sorbitan monostearate, NF			Sorbitan monostearate, NF	
Cetyl alcohol, NF			Cetyl alcohol, NF	
Stearyl alcohol, NF			Stearyl alcohol, NF	
White petrolatum, USP			White petrolatum, USP	
Propylparaben, NF			Propylparaben, NF	
Purified water, USP			Purified water, USP	
Glycerin, USP			Glycerin, USP	
Methylparaben, NF			Methylparaben, NF	
Xanthan gum, NF			Xanthan gum, NF	

*per OGD04-1043 regulatory review dated 3/24/05 and COMIS database

Reviewer's Comments: *The test formulation is qualitatively and quantitatively different from the reference product. The test product included (b)(4)% (w/w) oleic acid (b)(4) instead of the (b)(4)% (w/w) isostearic acid in the RLD. The test formulation also differs from the reference by more than (b)(4)% in the amounts of (b)(4)%), (b)(4)%), and (b)(4)%). All other remaining inactive ingredients are quantitatively the same.*

Oleic acid is an excipient in FDA-approved drugs, foods and cosmetics. Since the use of oleic acid in the amount of (b)(4)% in the test formulation is greater than the amount used in a previously approved drug product for topical administration, a Pharmacology/Toxicology consult was requested from the Division of Oncology Drug Products (DODP) to assess the safety of using oleic acid in the test formulation. On February 11, 2009, the consultant responded that the use of (b)(4)% oleic acid appears to be reasonably safe to include in the generic formulation of topical imiquimod cream. The consultant stated that the systemic exposure of oleic acid is expected to be low given that the maximal administered amount of (b)(4) oleic acid in the proposed test product is a small fraction of the 37000 mg/m^2 of oleic acid that is generally consumed by each person in a single day. No data is provided to establish whether the systemic absorption of imiquimod is altered by the use of (b)(4)% oleic acid instead of (b)(4)% isostearic acid (b)(4) in the test formulation.

According to the systemic absorption study in an NDA study (1402-IMIQ) conducted in 58 patients with AK, mean urinary recoveries of imiquimod and metabolites combined were less than 2% of the applied dose in patients using 75 mg (6 packets), 3 applications per week for 16 weeks. In 12 patients with genital/perianal warts, with an average dose of 4.6 mg, mean urinary recoveries of imiquimod and metabolites were less than 2.5% over the whole course of treatment. Considering the results of the NDA study in patients with AK, the extent of absorption of imiquimod following topical application to the skin with sBCC lesions were expected to be low. Based on the urinary excretion method for assessing the systemic bioavailability of imiquimod, the relative extents of absorption of topical imiquimod is estimated to be approximately 1% when applied on the face and scalp.[5]

A similar local safety and efficacy profile is seen in this clinical endpoint study between the test product and the reference product. The systemic absorption (1%) of imiquimod from topical use is known to be only approximately 1%. There are no known serious dose-related AEs associated with topical use of imiquimod. Therefore, any potential increase in systemic exposure of imiquimod with the use of (b)(4)% oleic acid in the test formulation is not likely to be clinically significant. The inactive ingredients in the proposed product are acceptable.

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA demonstrate that Nycomed's Imiquimod 5% Cream is bioequivalent to the reference listed drug, Graceway Pharmaceuticals' Aldara® Cream, 5%. The FDA statistical analysis concludes that the 90% CI of the difference in success (complete clearance of AK lesions) rate between the test and the reference products at visit 6/week 24 (8 weeks follow-up) in the PP population is (-0.094, 0.078), within the bioequivalence limits of (-

[5] Office of Clinical Pharmacology and Biopharmaceutics Review, NDA 20-723(S016), submission dated 6/9/03.

0.20 to +0.20). The test and reference products are also shown to be superior to vehicle at visit 6 in the MITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between the products.

B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 78-548, using the primary endpoint of success (complete clearance of AK lesions) rate at visit 6/week 24 (8 weeks follow-up), are adequate to demonstrate bioequivalence of Nycomed US Inc.'s Imiquimod 5% Cream, to the reference listed drug (RLD), Graceway Pharmaceuticals' Aldara® Cream, 5%. Both the test and the reference products also demonstrate superiority over vehicle in the modified intent-to-treat population at visit 6, demonstrating that the study is sensitive enough to detect differences between products.

_____ _____
Carol Y. Kim, Pharm.D. **Date**
Clinical Reviewer
Office of Generic Drugs

_____ _____
Dena R. Hixon, M.D. **Date**
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____
Dale P. Conner, Pharm.D. **Date**
Director
Division of Bioequivalence I
Office of Generic Drugs

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78548	ORIG-1	ALTANA INC	IMIQUIMOD

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

/s/

CAROL Y KIM
01/26/2010

DENA R HIXON
01/26/2010
I concur.

DALE P CONNER
01/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

STATISTICAL REVIEWS

Statistical Review

ANDA 78-548
Drug Product: Imiquimod Cream, 5%
Sponsor: Nycomed US Inc.
Reference Listed Drug: Aldara™ (NDA 20-723: 2/27/97), 3M Pharmaceuticals.
Recommended dosing regimens: apply twice daily for 28 consecutive Days.
Submission dates: October 2, 2007 and March 3, 2008.
Drug Class: Immune response modifier

Reviewer: Mohamed Nagem, DB6/OB/CDER
Requestor: Carol Kim, Pharm.D., OGD/CDER.

Remark: The data sets used in this analysis were supplied by the sponsor and received in the EDR on September 25, 2005.

Background

Actinic keratosis (AK), also known as solar keratosis, is the early beginnings of skin cancer that has the potential to progress to invasive squamous cell carcinoma (SCC). It may be difficult at times to make a clinical distinction between AK and SCC. An AK lesion may develop into SCC without any distinguishable clinical characteristics. Actinic keratosis lesions generally appear on sun-exposed areas of the face, ears, forearms, and hands. However, they can occur on the back, chest, and legs according to the level and frequency of sun exposure. Actinic keratosis lesions are usually flat and scaly. They range in size from 3 to 10 mm in diameter, and may enlarge into a larger, elevated lesion. Over the years, the lesions can gradually progress and approximately 5% of the lesions eventually develop into an invasive carcinoma.

Aldara ™ (imiquimod 5%) Cream is an immune response modifier approved for treatment of actinic keratosis (AK), superficial basal cell carcinoma (sBCC), and external genital warts. The mechanism of action of Aldara ™ Cream for treatment of AK and sBCC lesions is unknown.

Most patients using Aldara ™ Cream for treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with the recommended treatment regimen.

The following is a chronological summary of sponsor submissions and other related products which have been reviewed by the Office of Generic Drugs (OGD.)

1. INDs, Protocols (P), and/or Control Documents (CD) submitted by Nycomed US Inc.

Submission	Submission date	Comment
P04-034	6/23/04	Recommended a BE study in treatment of AK

2. INDs, Protocols (P), and/or Control Documents (CD) submitted by other sponsors

Submission	Submission date	Sponsor
P04-022	4/16/04	(b) (4)
CD 04-381	4/22/04	Teva
P04-040	8/6/04	Taro
CD04-1158	12/2/04	(b) (4)
P07-018	1/27/07 (review pending)	

3. Previous ANDA submissions for same or related product

None

Objectives of the study

The objectives of this study are to compare the safety and efficacy profiles of Nycomed US Inc's (Formerly Altana Inc.) Imiquimod Cream 5% to those of 3M Pharmaceuticals' Aldara™ (Imiquimod) Cream,
5%, and to demonstrate the superiority of the two active creams over that of the Nycomed US Inc.'s Placebo in the treatment of actinic keratosis.

Study Design

Study Design: This was a randomized, double-blind, parallel-group study design comparing the three products. Patients were randomized in a 3:3:1 (Test: Reference: Placebo) ratio to one of the three treatments twice daily for 28 Days (4 Weeks):

1. Test: Imiquimod Cream, 5%, Nycomed US Inc., lot #T045, manufactured on 6/29/05
2. Reference: Aldara ^{TM} Cream 5%, 3M Pharmaceuticals, lot #FG036A, expiration 7/06
3. Placebo (Vehicle): Nycomed US Inc., lot#T052

Patients were instructed to apply the assigned study medication prior to normal sleeping hours two times a week for 16 weeks. With each application, the cream was to be left on the skin for 6-10 hours. After at least 6 hours, but no more than 10 hours, patients were instructed to wash the application area with mild soap and water.

The study was designed to have each subject performing 6 visits. At Visit 1 (Day 1), an IRB-approved informed consent was obtained prior to any study related procedures being performed. The investigator performed a medical history, documented concomitant medications, performed a physical examination (height, weight, and vital signs), and evaluated subjects for AK. The investigator counted the AK lesions, recorded their location descriptively on an anatomical diagram in the Subject's source documentation, and measured the target treatment area's longest perpendiculars (height, width or length). A urine pregnancy test was performed for women of childbearing potential. Subjects who met inclusion/exclusion criteria were assigned to one of the

three study formulations in a 3:3:1 ratio and dispensed the next randomized unit of study medication by an independent third party dispenser not involved in clinical evaluations. Each subject number corresponded to a computer-generated randomized treatment group and medication kit. Subjects were instructed on medication application and completion of subject diaries. Subjects applied study medication topically 2 times per week for 16 weeks. The first application of study medication was made under the supervision of the third party study medication dispenser.

Subjects returned to the office for Visit 2 (Week 2/Day 14 ± 4 days/Interim), Visit 3 (Week 4/Day 28 ± 7 days/Interim), Visit 4 (Week 8/Day 56 ± 7 days/Interim), Visit 5 (Week 16/Day 112 ± 7 days/End of Therapy), and Visit 6 (Week 24/Day 168 ± 7 days/End of Study). At each visit, the subject's concomitant medications were updated and any adverse events recorded. The investigator counted all AK lesions, recorded their location descriptively on an anatomical diagram in the subject's source documentation, and noted if there were any new lesions since baseline. Compliance with drug applications was assessed and additional packets of study medication were dispensed. All study medication was collected at the end of therapy Visit 5. Subjects were required to return their diaries at each visit. If an investigator determined that a subject's condition may have been worsening, the investigator may have evaluated the subject during an unscheduled visit at any time, and unscheduled visit procedures would have been followed. If the investigator decided to discontinue a subject for one of the reasons listed below at any time during the study, a standard-of-care treatment may have been advised at the investigator's discretion. At that time, the study medication and diaries would have been collected, and an end of study Visit 6 performed. The Case Report Form (CRF) would also have been completed.

Subjects were removed from the study for any of the following reasons:

• If the subject withdrew his or her consent for any reason.
• If the subject's condition worsened to a degree that the investigator felt it was unsafe for the subject to continue in the study.
• If the subject's study drug code was unblinded.
• If an adverse event (AE) occurred for which the subject desired to discontinue treatment or the investigator determined that it was in the subject's best interest to be discontinued.
• If there was a significant protocol violation.
• If a concomitant therapy was reported or required which was liable to interfere with the results of the study.
• If the subject missed more than six consecutive study medication applications.
• If the subject was lost to follow-up. The investigator documented efforts to attempt to reach the subject twice by telephone and sent a certified follow-up letter before considering the subject lost to follow-up.
• If the subject became pregnant.
• Administrative reasons.

Table 9.1: Study Schedule

Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/ End of Therapy**	**Visit 6/ End of Study**	**Unscheduled Visit**
Visit Day	**Day 1 (Baseline)**	**Day 14 (± 4) Week 2**	**Day 28 (± 7) Week 4**	**Day 56 (± 7) Week 8**	**Day 112 (± 7) Week 16**	**Day 168 (± 7) Week 24**	
Screening/Consent	X						
Demographics	X						
Medical History	X						
Physical Exam (including vital signs)	X						
Urine Pregnancy Test *	X						
Inclusion/Exclusion Criteria Review	X						
Assessment of Diagnosis of Actinic Keratosis	X						
Actinic Keratosis Counts	X	X	X	X	X	X	X
Local Skin Reactions/ Irritation	X	X	X	X	X	X	X
Adverse Event Reporting		X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Drug Dispensing	X	X	X	X	X		
Subject Instruction/ Compliance Review	X	X	X	X	X	X	X
Drug Return, Accountability		X	X	X	X	X	If applicable

* For females of child-bearing potential – to be completed in doctor's office prior to enrollment.

Outcome Variables

1. The local skin reactions were evaluated for intensity at each visit using the following four-point scale (0-3):

Erythema: redness
0=none; no visible pink or red
1=mild; faint pink tone
2=moderate; pink to red tone
3=severe; definite distinct red tone

Scabbing/crusting: a crust formed and covered a healing lesion
0=none; no scabs or crusts
1=mild; few small areas of scabbing/crusting seen on close exam
2=moderate; larger areas of scabbing/crusting; easily noticeable
3=severe; widespread areas of scabbing/crusting noticed at first glance

Flaking/scaling/dryness: dry, thin flakes, or sheets of epidermis shedding from the Skin
0=none; no flaking/scaling/dryness
1=mild; slight flaking/scaling/dryness seen on close exam only
2=moderate; distinct flaking/scaling/dryness; easily noticeable
3=severe; marked/intense heavy flaking/scaling/dryness notices at first glance

Erosion/ulceration: destroyed skin surface; lesion with pus and necrosis of surrounding tissue
0=none; no erosion/ulceration
1=mild; small superficial erosion/ulceration seen only on close exam
2=moderate; more prominent, distinct erosion/ulceration easily noticeable
3=severe; marked/intense, widespread erosion/ulceration noticed at first glance

Primary Endpoints:

The primary endpoint of this study was the Complete Clearance Rate of the actinic keratosis in the treatment area. Complete clearance was defined by the sponsor as a post treatment count of zero (0) clinically visible AK lesions in the treatment area at visit 6/week 24 (8 weeks follow-up).

Secondary Endpoint:

The sponsor evaluated the proportion of patients who achieved Partial Clearance of actinic keratosis lesions in the treatment area as a secondary endpoint. Partial clearance was defined as having a 75% or greater reduction in the clinically visible AK lesions in the treatment area compared to visit 1 (baseline). The secondary efficacy outcome was evaluated at visit 6/week 24 (8 weeks follow-up).

The Subgroup Analyses: The OGD Clinical reviewer requested that a subgroup analysis of complete clearance by Fitzpatrick skin type (type I and II: Fair vs. type III through V: Medium) be conducted for the MITT and PP populations to determine the significance between the treatment groups.

Analysis Populations

Three patient populations were defined by the sponsor as follows:

The intent-to-treat (ITT) population: Includes all patients randomized to treatment who used at least 1 dose of the study drug.

Two populations will be evaluated for efficacy and equivalence:

Modified-Intent-to-Treat population (MITT): – Includes all randomized subjects who met the inclusion/exclusion criteria, had 4-10 definite, visible, discrete, nonhyperkeratotic, nonhypertrophic, clinically diagnosed AK lesions located within a contiguous 25-cm2 treatment area on the face or balding scalp received at least one application of study medication, and had at least one post-baseline efficacy evaluation.

Per Protocol population (PP): includes all randomized subjects in the MITT population who met the following criteria:

- Took between 70% -120% of expected study medication applications.
- Had not taken any concomitant medications prohibited by the protocol and had no other significant protocol violations,
- Did not miss more than 6 consecutive study medication applications AND returned for visit 6/end of study within the visit windows and had data on the primary efficacy variables for all clinical evaluations OR met per protocol criteria up to the time of early study discontinuation due to treatment failure after applying study medication for at least 12 weeks (with a compliance rate of 70%).

For the analyses of efficacy, the primary analysis was based on the MITT population and the Last Observation Carried Forward (LOCF) approach was used to impute missing data in the MITT population. However a subject who did not have a post-baseline visit evaluation was excluded from analyses. In the PP population, the LOCF approach was used only for patients who discontinued due to treatment failure.

Statistical Analysis Methods

Efficacy Analysis

The efficacy analyses for the Complete Clearance Rates (success/failure) were carried out by using Fisher's exact test. The efficacy analysis for each active treatment was conducted separately by comparing its rate to that of the vehicle.

Equivalence Analysis

Based on the usual method used in the OGD for binary outcomes, the 90% confidence interval for the difference in proportions between the Test and Reference treatments should be contained within -.20 to .20 in order to establish equivalence.
The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$, or $p_T - p_R > .20$ versus H_A : $-.20 \leq p_T - p_R \leq .20$
where p_T = Cure rate of the Test product, $\hat{p}_T$ = Sample success rate of the Test product,
p_R = Cure rate of the Reference product, $\hat{p}_R$ = Sample success rate of the Reference product.

Let n_T = sample size of Test treatment n_R = sample size of Reference treatment

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between Test and Reference was calculated as follows, using Yates' correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$, $U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$,

We reject H_0 if $L \geq -.20$ and $U \leq .20$.
Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

Statistical Analysis Results

Baseline characteristics:

A total of 564 patients was enrolled in the study, 240 in the Test product group, 242 in the Reference product group and 82 in the Vehicle product group. Of these, five hundred forty seven (547) were qualified to be included in the MITT population (235 subjects were in the Test group, 232 were in the Reference group and 80 were in the Vehicle group). The PP population based on baseline entry criteria and the PP definition comprised 203 patients in the Test product group, 199 patients in the Reference product group and 72 in the Vehicle group. Table 1 describes the ITT, MITT, and PP population distributions.

Table 1 - Population distributions

Population	Test (N = 240)	Reference (N = 242)	Vehicle (N = 82)	Total (N = 564)
Subjects In the ITT	240 (100%)	242 (100%)	82 (100%)	564 (100%)
Patients Excluded from MITT	5 (2%)	10 (4%)	2 (2%)	17 (3%)
Total Patients in the MITT	235 (98%)	232 (96%)	80 (98%)	547 (97%)
MITT Patients Excluded from PP	32 (13%)	33 (14%)	8 (10%)	73 (13%)
Total Patients in the PP	203 (85%)	199 (82%)	72 (88%)	474 (84%)

Demographic characteristics

According to the sponsor, all the enrolled patients at baseline consisted of 547 (100%) who are white, however one subject also marked he/she was of other races. The mean age of patients was 67, and the mean age was comparable among the treatment groups (p-value = 0.78). Table 2 describes the demographic characteristics for the population.

Table 2 - Demographic characteristics of the MITT population

Parameter	Test (N = 235)	Reference (N = 232)	Vehicle (N = 80)	p-Value
Age [1]				
MAX	93	85	85	
MEAN	66	67	67	
MIN	35	40	41	0.78
N	217	213	79	
STD	10	10	10	
Gender [2]				
Male	197 (81.4%)	198 (82.5%)	72 (87.8%)	0.41
Female	45 (18.6%)	42 (17.5%)	10 (12.2%)	
Race [3]				p-value
White	235 (100%)	232 (100.0%)	80 (100%)	1.00
Others	(0%)	(0.0%)	(0%)	

[1] p-value for treatment comparisons based on a two-way analysis of variance model with factors of treatment and site.
[2] Cochran-Mantel-Haenszel Statistics for General Association (Based on Table Scores).
[3] All patients are white, however, one subject also marked he/she was of other races.

The total number of AK lesions present at baseline ranged from 4-12 lesions, with a mean of 5.73 ± 1.73. The treatment groups were comparable for all demographic characteristics in the MITT population. The test for homogeneity in number of AK lesions at baseline yields a p-value of 0.97. Table 3 summarizes the baseline AK lesions in the MITT population from this reviewer's perspective.

Table 3- Baseline AK lesions distribution in the MITT population

Total number of AK lesions at baseline	Test (N = 235)	Reference (N = 232)	Vehicle (N = 80)	p-value[1]
MEAN	5.71	5.74	5.75	0.97
STD	1.63	1.72	1.83	
MIN	4	4	4	
MAX	10	12	11	

[1] The p-value is based on an ANOVA model

Efficacy and equivalence analyses:

The efficacy analyses based on the Complete Clearance rate at visit 6 (primary endpoint) showed the superiority of the Test and Reference products over that of the Vehicle's response rate in the MITT population (Table 4). The two-sided Fisher's exact test yields p-values < 0.001. In addition, comparisons based on the Partial Clearance rate at visit 6 (secondary endpoints), the Test and the Reference product group response rates were statistically significantly better than the vehicle. The two-sided Fisher's exact test yields a p-value less than 0.001 for the Partial Clearance rate at visit 6 in the MITT population. Table 4 summarizes the efficacy results based on the primary and secondary endpoints.

Table 4- Efficacy Analyses

Parameter	MITT Population			p-value [1]	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Complete Clearance Rate at visit 6	40% (94/235)	43% (100/232)	19% (15/80)	< 0.001	< 0.001
Partial Clearance Rate at visit 6	49% (116/235)	54% (125/232)	26% (21/80)	< 0.001	< 0.001

[1] p-values for treatment groups comparisons based on the two-sided Fisher's exact test.

In addition subgroups analyses by Fitzpatrick skin type for Complete Clearance rate and Partial Clearance rate at visit 6 showed supportive evidence of superiority of the Test and Reference products over the vehicle in the subgroup of subjects with Fitzpatrick skin type of Fair; however the statistical test failed to show superiority of the Test and Reference product group over the Vehicle in the subgroup of subjects with Fitzpatrick skin type of Medium. Table 6 summarizes the efficacy results based on the subgroup analyses.

The Test and Reference products were found to be clinically equivalent for Complete Clearance rate at visit 6 (primary endpoint) and for Partial Clearance rate at visit 6 (Secondary endpoint) in the PP population. In addition, Complete Clearance rate and Partial Clearance rate at visit 6, by Fitzpatrick skin type of Fair vs. Medium all showed supportive evidence of bioequivalence across these subgroups. Table 5 summarizes the Clinical equivalence results in the PP population.

Table 5- Bioequivalence Analyses

Parameter	PP Population			
	Test	Reference	The 90% CI for the Test and Reference	Is the 90% CI within [-20%,20%]?
Complete Clearance Rate at visit 6	42% (85/203)	43% (85/199)	(-9.4 , 7.8)	YES
Partial Clearance Rate at visit 6	50% (102/203)	55% (109/199)	(-13.2 , 4.2)	YES

Table 6- Subgroup Analyses by Fitzpatrick skin type

Parameter	**MITT Population**			**p-value**	
Subgroup Efficacy analyses (By Skin Type): Mitt Population	Test	Reference	Vehicle	Test Vs. Vehicle	Reference Vs. Vehicle
Complete Clearance Rate at visit 6 for Skin Type I and II (Fair)	41% (56/136)	49% (73/150)	15% (8/52)	< 0.001	< 0.001
Partial Clearance Rate at visit 6 for Skin Type I and II (Fair)	50% (68/136)	59% (89/150)	25% (13/52)	0.0028	< 0.001
Complete Clearance Rate at visit 6 for Skin Type III through V (Medium)	38% (38/99)	33% (27/82)	25% (7/28)	0.2636	0.4864
Partial Clearance Rate at visit 6 for Skin Type III through V (Medium)	48% (48/99)	44% (36/82)	29% (8/28)	0.0841	0.1839
Subgroup Equivalence analyses (By Skin Type): PP population	Test	Reference	The 90% CI for the Test and Reference	Is the 90% CI within (-20%, 20%)?	
Complete Clearance Rate at visit 6 for Skin Type I and II (Fair)	44% (52/118)	48% (61/127)	(-15.3 , 7.3)	YES	
Partial Clearance Rate at visit 6 for Skin Type I and II (Fair)	53% (62/118)	61% (77/127)	(-19.3 , 3.1)	YES	
Complete Clearance Rate at visit 6 for Skin Type III through V (Medium)	39% (33/85)	33% (24/72)	(-8.4 , 19.4)	YES	
Partial Clearance Rate at visit 6 for Skin Type III through V (Medium)	47% (40/85)	44% (32/72)	(-11.8, 17.0)	YES	

Comments on the Sponsor's Analyses

The Sponsor's primary efficacy variable was Complete Clearance rate at visit 6 (Week 24). Based on the sponsor's statistical analysis using 90% confidence intervals, the study demonstrates that the difference in the Complete Clearance rates between the Test and the Reference products is within [-.20, +.20] .

The sponsor's analyses, while giving a similar conclusion with regard to efficacy and bioequivalence for the primary endpoint, were based on a different MITT and PP population than that considered by this reviewer.

Because the sponsor inappropriately included and/or excluded some patients, or classified some patients as treatment success when they should have been considered a failure, the FDA Medical reviewer requested a re-evaluation of the sponsor's data with the changes as described in the Medical review (page 29 of the Medical review).

Table 7. Primary Efficacy Analysis: Complete Clearance of AK lesions at visit 6/week 24 (8 weeks follow-up); per sponsor

					p-values	
Parameter	**Reference**	**Test**	**Vehicle**	**90% C.I. for Bioequivalence of Test to Reference**	**Reference vs. Vehicle**	**Test vs. Vehicle**
Per-Protocol Subjects (n,%)						
	(N=198)	(N=201)	(N=72)			
Complete Clearance	85 (42.9%)	85 (42.3%)	15 (20.8%)	-8.00% to 9.29%	0.001[2]	0.002[2]
Failure	113 (57.1%)	116 (57.7%)	57 (79.2%)			
Modified Intent-to-Treat Subjects (n,%)						
	(N=239)	(N=238)	(N=81)			
Complete Clearance	101 (42.3%)	95 (39.9%)	15 (18.5%)	-5.48% to 10.17%	<0.001[2]	<0.001[2]
Failure	138 (57.7%)	143 (60.1%)	66 (81.5%)			

Note: Missing efficacy results were replaced using an LOCF approach for mITT subjects who were discontinued early due to treatment failure.

[1] Confidence interval calculated using Wald's method with Yates' continuity correction.

[2] P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Conclusion

Efficacy:

Our analysis showed that the Test and the Reference products' Complete Clearance rates at visit 6 (primary endpoint) in the MITT population were statistically significantly superior to the Vehicle rate in the treatment of actinic keratosis (AK).

Secondary analyses based on the dichotomized Partial Clearance rates at visit 6 showed that the responses to the active treatments were statistically significantly better than those of the vehicle in the MITT population.

Equivalence: The Test and Reference products were found to be Clinically equivalent for both endpoints – Complete Clearance rate at visit 6 (primary endpoint), Partial Clearance rate at visit 6 - in the PP population.

For the subgroup analyses of Fitzpatrick skin type (Fair vs. Medium), while the test statistics showed superiority of both the Test and Reference product groups over Vehicle product group in the Fitzpatrick skin type of Fair, the same test failed to show superiority of the Test and Reference product groups in the Fitzpatrick skin type of Medium subgroup.

The test statistics for Clinical equivalence showed the that Test and Reference product groups were equivalent in the two subgroups -- Fitzpatrick skin type of Fair and Fitzpatrick skin type of Medium.

Mohamed Nagem
Mathematical Statistician, DB6/OB

Donald J. Schuirmann
Expert Mathematical Statistician, DB6/OB

_____

Stella G. Machado, Ph.D.
Director, DB6/OB

cc: Original ANDA 78-548
HFD-600 Dena Hixon, Carol Y. Kim, Debra Catterson
HFD-700 S. Lillian Patrician, MS, MBA
HFD-705 Stella Machado, Donald J. Schuirmann, Mohamed Nagem

This Review Includes 12 pages.

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

/s/

Mohamed Nagem
1/17/2009 11:31:08 AM
BIOEQUIVALENCE STATISTICIAN

Donald Schuirmann
1/21/2009 08:13:17 AM
BIOMETRICS

Stella Machado
1/30/2009 01:00:12 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

OTHER REVIEWS

CONSULTATION REPLY

DATE: February 11, 2009

FROM: Robert T. Dorsam, Ph.D. Pharmacologist, DDOP, Office of Oncology Drug Products

TO: Office of Generic Drugs
RE: ANDA #78-548
SUBJECT: Oleic acid ((b) (4) in imiquimod Cream (5%)
DRUG NAME: Imiquimod Cream
FORMULATION: Topical
APPROVED INDICATIONS:

- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.
- External genital and perianal warts/condyloma acuminata in patients 12 years old or older.

SPONSOR: Altana Inc.

Background:
An ANDA for a generic formulation of imiquimod cream (5%) is currently being reviewed by the Office of Generic Drugs for its bioequivalence with the FDA-approved topical drug Aldara. The proposed generic formulation of imiquimod contains (b) (4) oleic acid. The FDA has currently approved topical agents that contain up to 7.4% oleic acid. The Office of Generics has consulted the Division of Drug Oncology Products about the safety of (b) (4) oleic acid in the imiquimod cream.

Oleic acid ((Z)-9-Octadenoic acid), CAS #112-80-1, has a molecular formula of $C_{18}H_{34}O_2$, a formula weight of 282.46 and a density of 0.895. It is a colorless to light yellow liquid that is found in many vegetable oils, food additives, animal fats, shampoos, lotions and cosmetics. Meat, poultry, and fish are also major sources of oleic acid. Olive oil, peanut oil, teaseed and pecan oil contain 60-80% oleic acid, while cosmetics contain up to 25% (CIR 1987). Oleic acid is a "Generally Recognized as Safe" (GRAS) substance as a food additive which has no limitation with regard to its use as an additive. Americans who submitted to a 3-day dietary survey by the U.S Department of Agriculture consumed 20-30 grams/day (≈ 12.3 to 18.5 g/m^2) of oleic acid, comprising 91-95% of the total mono-unsaturated fats consumed by the study group (Jonnalagadda et al., 1995). In the U.S. food supply, oleic acid rose from 56 grams (≈ 34.5 g/m^2/day) per capita per day in 1980 to 68 grams (≈ 42 g/m^2/day) in 2000 (Gerrior et al., 2004).

Corresponding with its increase in the food supply, oleic acid intake increased from 45 g/day (≈ 27.8 g/m^2/day) in 1913 to 60 g/day (≈ 37 g/m^2/day) in 1980 (Marston, 1986). Aside from its dietary use, oleic acid is used as an inactive ingredient in FDA-approved drugs that are inhalants, nasal sprays, oral tablets, topical solutions and transdermal patches.

In this preparation, oleic acid is (b) (4) (b) (4). Oleic acid is an 18-carbon mono-unsaturated fatty acid in the cis configuration. These structural elements allow oleic acid to insert into the lipid membrane and reduce the tight packing of saturated membrane lipids. Topically applied oleic acid can be measured in epidermal layers of the skin 10 minutes after its application (CIR 1987). Oleic acid alters the lipid domains of the stratum corneum to (b) (4) and has been used in many topical drug formulations though several other fatty acids of varying chain length and saturation are also used for this same purpose. Isostearic acid is a C_{18} fatty acid that is used in the innovator drug Aldara. A clinical study performed by the sponsor demonstrates that Nycomed US Inc.'s imiquimod 5% cream is bioequivalent to Aldara.

Imiquimod, the active ingredient of Aldara, is an immune activator currently approved for the topical treatment of actinic keratosis, genital/perianal warts and superficial basal cell carcinoma. While the mechanism of action is currently unknown, some publications suggest that imiquimod binds to the Toll-like receptor 7 on dendritic cells to activate an immune response and cytokine release at the site of administration (Miller et al., 2008). These studies propose that the immune system attacks viral-infected cells that comprise the wart or carcinoma, resulting in their removal and eventual reduction of the lesion. Itching, burning and pain are the most common side effects, along with erythema, scabbing, flaking and edema at the site of administration.

Toxicity:

Both acute and chronic toxicity studies for topical oleic acid illustrate mild to moderate skin effects at the site of administration (study summaries from CIR 1987 and TOXNET). Toxicities associated with dermal application of commercial-grade oleic acid were limited to skin irritation with crusting, ulceration, and thickening of skin in rabbits (2 mL), guinea pigs (1 mL) and mice (0.3 mL). Microscopic findings included hyperkeratosis, pronounced acanthosis, follicular keratotic plugs, hyperplasia of sebatious glands and hair shaft loss. Intradermal injection of 0.1 mL of 25, 50 and 75% oleic acid to the backs of guinea pigs caused local skin inflammation and necrosis. Topical administration of 1 mL 50% oleic acid to mice resulted in epidermal hyperplasia and hyperkeratosis. When 3 mL of 5% oleic acid was applied daily for 5 days/week over 6 weeks to the outer ear canal of albino rabbits, slight erythema was followed by desquamation. Follicular keratosis occurred at 1 month, and persisted 6 weeks post-treatment. In another test, 5% oleic acid did not sensitize the skin after repeated exposures. A cosmetic mascara product containing 2-5% oleic acid (0.1 mL) caused no or slight conjunctival irritation in rabbit eyes, and application of a 6% oleic acid formulation of mascara produced no irritation to the eyes of rhesus monkeys. Most

studies did not report the skin surface area that was exposed to topical oleic acid, therefore the extent of exposure could not be assessed. In consideration of these data, oleic acid appears to be a mild skin and eye irritant.

The no-observed-effect-level (NOEL) for oral oleic acid in mice is 150 mg/kg/day (≈ 450 mg/m^2/day) and 100 mg/kg/day (≈ 600 mg/m^2/day) in rats, while the no-observed-adverse-effect-level NOAEL is reported to be ≤ 1000 mg/kg (≈ 6000 mg/m^2) in rats. (Munro and Kennepohl, 2000; IUCLID dataset, 2000). The LD_{50} for is 28 g/kg (≈ 84 g/m^2) in mice and 25 g/kg (≈ 150 g/m^2) in rats (MSDS). Other related fatty acids have a similarly high LD_{50} value. The LD_{50} for mice with i.v. oleic acid was 230 mg/kg (≈ 690 mg/m^2)(MSDS). Oral doses of 10 and 21.5 mL/kg (≈ 53.7 and 115.5 g/m^2, respectively) of commercial grade oleic acid did not cause mortality but caused depressed righting reflexes, oily and unkempt fur, mucoid diarrhea, salivation and serosanguineous discharge from the mouth and eyes of rats (CIR 1987). Topical administration of oleic acid results in "minute" plasma levels (CIR 1987), so studies with oral and intravenous administration provide exposure levels that are several orders of magnitude above the exposure from topical application of this formulation (See Table 1). The acute toxicity from oral administration of oleic acid and other fatty acids are minimal.

Summary of Exposure of Oleic Acid

Oleic acid dose mg/m^2*	Species	Description
15	Mouse	Not carcinogenic
38	Human	Potential human exposure with proposed drug product
75	Mouse	1 mammary carcinoma at 9 months
450	Mouse	NOEL
600	Rat	NOEL
690	Mouse	LD50, i.v.
≤ 6000	Rat	NOAEL
18,000	Human	Daily intake (3-day USDA study)
37,000	Human	Daily intake
42,000	Human	Per capita in food supply
53,000 - 115,000	Rats	Depressed righting reflexes, oily and unkempt fur, mucoid diarrhea, salivation, discharge from mouth and eyes
84,000	Mice	LD_{50}
150,000	Rats	LD_{50}

*All doses of oleic acid are by the oral route, except where noted.

In mutagenesis studies, oleic acid was cytotoxic to five Salmonella strains but did not revert any of the tester strains and therefore was not mutagenic in these experiments. Another study illustrated that oleic acid can inhibit the mutagenic activity of compounds in a modified Ames test. Oleic acid (100 to 500 µg/mL) increased aneuploidy in *S. cerevisiae* without affecting the number of mitotic cross-over events, and also caused aneuploidy in V79 Chinese hamster lung fibroblasts at doses of 2, 5 and 10 µg/mL. In carcinogenicity tests, mice that received 10 injections of 0.1 mg oleic acid (≈ 15 mg/m^2)

over 3 weeks did not have increased incidence of neoplasms in the 9 (of 15) mice that survived 1 year. Of 16 mice injected twice weekly with 0.5 mg (≈ 75 mg/m^2) for 33 injections, one mammary carcinoma was evident after 9 months. Another study in which benzoapyrene and 25 mg of oleic acid in acetone were applied 3 times a week for 440 days showed no benign or malignant skin tumors.

Female rats fed oleic acid (15%) for 10 to 16 weeks had no adverse effects, and all were fertile subsequent to the diet. In a second study, 7 female rats were fed 15% oleic acid for 16 weeks and maintained fertility. Out of 52 pups, 44 survived 1 week and 11 survived 3 weeks. Mammary development was retarded and was suspected to be the source of poor litter survival. Oleic acid passes the placental barrier in rabbits, guinea pigs, rats and humans (CIR 1987) and also transfers to maternal milk (Fidler et al., 2000). Teratogenicity of oleic acid has not been assessed.

CONSULTATION REPLY AND CONCLUSIONS TO THE QUESTIONS SUBMITTED:

Question: Firm has proposed to use (b) (4) oleic acid in a topical product. This is greater than used in a previously approved drug product. Is (b) (4) oleic acid safe for use in a topical formulation?

Oleic acid is an excipient in many FDA-approved drugs and is widely used in foods and cosmetics, therefore extensive systemic and dermal exposure has occurred in humans over decades. Administration of the proposed generic drug product will expose the patient to (b) (4) mg oleic acid per day (≈(b) (4) mg/m^2/day) for use 3 to 5 times per week. While oleic acid penetrates the epidermal barrier, absorption into the blood and the resulting systemic exposure is expected to be low. Even maximal systemic exposure of (b) (4) mg/m^2 oleic acid from the proposed generic product would represent a small fraction of the 37000 mg/m^2 of oleic acid that is consumed by each person in a single day in the U.S. Clinical bioequivalence was established between Aldara and the proposed generic product. In consideration of these factors, (b) (4) oleic acid appears to be reasonably safe to include in the generic form of imiquimod.

RECOMMENDATION:

In consideration of the extensive human experience and non-clinical data, (b) (4) oleic acid appears to be reasonably safe to include in the generic form of imiquimod.

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TOXNET: http://toxnet.nlm.nih.gov/

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: June 15, 2009

From: Brenda Carr, M.D./Medical Officer, Dermatology

Through: Jill Lindstrom, M.D./Team Leader, Dermatology
Susan Walker, M.D./Director, Division of Dermatology and Dental Products

To: Dena Hixon, M.D./Associate Director for Medical Affairs
Office of Generic Drugs

CC: Julie Beitz, M.D., Director, ODE 3, CDER
Maria R. Walsh, RN, MS, Acting ADRA, ODE 3, CDER

Re: DDDP Consult #1144

Materials Evaluated: Aldara label (approval date March 22, 2007), Efudex label (approval date October 13, 2005) Agency Response to Citizen Petition 2004P-0557/CP1 (submitted by Valeant Pharmaceuticals, manufacturer of Efudex)

Background: The Office of Generic Drugs (OGD) is preparing to post guidance on the determination of bioequivalence of generic versions of imiquimod cream, 5% to the reference listed drug (RLD), Aldara Cream, 5%. The OGD is requesting comments from the Division of Dermatology and Dental Products (DDDP) on the recommended study design and endpoints for a clinical bioequivalence study prior to posting the recommendations on the Guidance Documents Web Page. Additionally, OGD seeks DDDP comment on these recommendations prior to taking action on ANDA 78-548 for imiquimod cream, 5%.

ANDA 78-548 was submitted October 17, 2006. The DDDP was consulted on March 16, 2009, however, due to an administrative oversight, the consult was not received by DDDP until April 3, 2009. It appears that, by agreement with OGD, the sponsor of ANDA 78-548 conducted one comparative clinical study which evaluated imiquimod in

the treatment of actinic keratoses. The OGD has concluded that "the application is acceptable for approval from a regulatory and CMC perspective" (p. 5 of the consult request).

Aldara (imiquimod) Cream 5% is indicated for the topical treatment of:

1. clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults,
2. biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.
3. external genital and perianal warts/condyloma acuminata (EGW) in patients 12 years old or older.

The OGD stated in their consult that "(w)hen the reference drug product is approved for more than one indication with the same site of pharmacologic activity, bioequivalence is generally established with a single study in the indication that is most likely to discern differences between the generic and reference products. If the product is determined to be bioequivalent for that indication, it is also considered bioequivalent for other indications with the same site of action" (p. 3 of the consult request).

Comment: *For imiquimod, the shared sites of action for the three indications are the epidermis and papillary (upper) dermis, since all of the lesions are epidermal and can or do extend into the papillary dermis. However, actinic keratoses do not typically extend into the dermis.*

Spear Pharmaceuticals (Spear) developed a generic 5-fluorouracil (FU) cream, 5%. The RLD, Efudex Cream, is indicated for "multiple actinic or solar keratoses" and "superficial basal cell carcinomas (sBCC) when conventional methods are impractical, such as with multiple lesions or difficult treatment sites." Per the consult request (p. 4), based on advice from OGD, Spear conducted one clinical bioequivalence study evaluating their 5-FU cream in the treatment of actinic keratoses; study of sBCC was not requested. Based on the results of the actinic keratoses study, the Spear's generic 5-FU product was approved for both multiple actinic or solar keratoses and sBCC (ANDA 77-524).

The OGD applied the framework used for establishing bioequivalence in the development of a generic 5-FU 5% cream to development of a generic imiquimod 5% cream. The OGD believes that for imiquimod, the actinic keratoses indication "is likely to be the most sensitive in detecting a difference between the test and reference products" and cite the following as their reasons (p. 4):

- All patients receive the same treatment for the same duration with assessment of primary efficacy 8 weeks after the end of treatment.
- The clinical diagnosis is straightforward.
- The treatment site is easily accessible for application of study product and assessment of treatment response.

- No differences in success rates have been reported for different patient populations.
- The success rates are lower than those of the other two indications.

Thus, OGD has recommended that one clinical comparative study be conducted in actinic keratoses to establish bioequivalence of a generic imiquimod cream, 5% to the RLD, Aldara™ cream. Per p. 5 of the consult, "(t)hese recommendations have been provided to a number of generic sponsors in response to controlled correspondences."

Comment: *Unless otherwise indicated, "AK"in this consult specifically refers only to the type of acinic keratoses for which imiquimod is indicated, i.e. "clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses."*

Consult Reply:

In our opinion, the thinking applied to development of a generic 5-FU cream may not entirely translate to development of a generic imiquimod cream. We note the following statement on p. 9 of the response to Citizen Petition 2004P-0557/CP1:

"…(T)he Agency concludes an AK bioequivalence study is sufficient to establish that the generic topical 5-FU formulation will be available in the epidermis and the upper dermis to act on both AK and sBCC lesions to an extent that is comparable to Efudex Cream."

Importantly, however, we also note the following footnote to the above statement (p. 9):

"We note that this conclusion is based on the specific characteristics of this topical product (5-FU) and the indications at issue. Factors involved in the assessment of other topical products may warrant a different result."

We in the DDDP agree and believe that issues unique to imiquimod may warrant recommendations different from those given for development of generic topical 5-FU products. Specifically, we recommend that the indication that should be studied in a clinical bioequivalence study in development of generic imiquimod products be superficial basal cell carcinoma.

Discussion:

The Citizen Petition response included discussion of the thickness of the stratum corneum in actinic keratoses relative to that of sBCC. However, the extent to which that discussion might apply to imiquimod is unclear, since imiquimod and 5-FU have different actinic keratoses indications.

Imiquimod is specifically indicated for nonhyperkeratotic, nonhypertrophic AK (emphasis added), a sub-type of actinic keratoses to which 5-FU is not restricted. Topical 5-FU has the broader indication of "multiple actinic or solar keratoses," i.e. there is no restriction relating to hyperkeratosis (thickened stratum corneum). A 5-FU product could, in fact, be used for hyperkeratotic and/or hypertrophic actinic keratoses, i.e. lesions with particularly thick stratum corneum and lesions for which imiquimod is not

indicated. Stratum corneum thickness would not be as much at issue in an imiquimod development program, given the limitations of the AK indication (i.e. nonhyperkeratotic, nonhypertrophic lesions). Also, we are not aware that the typical clinical presentation of sBCC is necessarily with an extensively compromised stratum corneum (as is suggested, in our opinion, in the Citizen Petition response, e.g. p. 8). To our knowledge, there may be areas of erosion, but there may also be areas of scaling (hyperkeratosis), to an extent that some lesions may be described as "psoriasiform" (psoriasis like). We note too that the skin barrier may be compromised in the setting of actinic keratoses, i.e. erosions may be present in the field of actinic keratoses. Thus, a thickened stratum corneum may not be unique to AK, and a compromised stratum corneum may not be unique to sBCC.

Another factor which must be considered is that, unlike 5-FU, imiquimod is also indicated for external genital warts, a sexually-transmitted disease of viral etiology. We note too that prominent acanthosis (thickened epidermis) is an additional feature that sets this indication apart from AK and sBCC. Further, because of the location, this indication makes for occlusive conditions of use with the potential for increased systemic exposure, relative to the other two indications.

For topically administered products not intended for systemic absorption, bioequivalence cannot be established by pharmacokinetic methods and must be established in well-controlled clinical trials.

Imiquimod has three labeled indications:

- clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.
- biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.
- external genital and perianal warts/condyloma acuminata in patients 12 years or older.

On p. 4 of the consult request, OGD states that, "(t)he most sensitive clinical endpoint bioequivalence study design is generally conducted in an indication with the least inherent variability, using the lowest recommended treatment dose and/or duration, and the earliest evaluation time at which a significant treatment effect is expected." In our opinion, several factors suggest that for imiquimod, sBCC would be the indication that would be most sensitive in discerning a difference between a generic product and the RLD in a clinical bioequivalence study:

1. Of the three indications, sBCC would have the least variability in the disease state and expected disease course, since labeling limits treatment to one lesion with an upper limit diameter of 2.0 cm, and this sub-type of BCC has a relatively consistent clinical presentation. Additionally, sBCC is not generally reported to spontaneously remit (although it may). In the consultant's experience spontaneous remission is more likely/commonly seen with AK and EGW.
2. At 6 weeks (30 doses total), the duration of treatment for which a significant treatment effect is expected is shortest for sBCC, and the duration of treatment is the same for all patients. We make a distinction between the duration of treatment (6 weeks) and the timepoint of efficacy assessment (12 weeks post-

treatment): it is the 6 weeks of treatment that makes for the effect assessed at Week 18. The duration of treatment may be > twice as long for the EGW (up to 16 weeks; maximum of 48 doses) and AK (16 weeks; 32 doses) indications.

3. In a comparative clinical bioequivalence trial of imiquimod in the treatment of sBCC, drug delivery to the sites of action (epidermis and papillary dermis) would be assessed by both clinical and histological endpoints. Outcomes would be assessed only clinically for AK and EGW which might be relatively less sensitive measures of assessing treatment outcomes. That addition of histological assessment makes for a more sensitive measure than does clinical assessment alone is evidenced by the fact that 6% of Aldara-treated subjects "who appeared to be clinically clear had evidence of tumor on excision of the clinically-clear treatment area" (see Clinical Studies section of Aldara label).

Although the success rates in the clinical trials supporting NDA approval for imiquimod in the treatment of sBCC were the highest of all three indications (see Aldara label), so too was the bar for establishing success, i.e. the composite endpoint of clinical and histological clearance.

Conclusions:

If approved, a generic imiquimod cream would be indicated for treatment of premalignant lesions (actinic keratoses), a nonmelanoma skin cancer (superficial basal cell carcinoma) and a sexually-transmitted infectious disease (external genital warts). If approval of a generic imiquimod product is to be based on study of one indication, we believe the public health would be best served were bioequivalence established in the indication which had the most stringent criteria for assessing outcomes. We believe that the indication which had the most stringent criteria for assessing outcomes would be the most sensitive in discerning a difference between the generic product and the RLD. For imiquimod, we believe this indication to be superficial basal cell carcinoma.

We recommend that the Guidance for Industry on development of generic versions of imiquimod cream, 5% suggest that superficial basal cell carcinoma be the indication studied.

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/s/

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MEDICAL OFFICER

Susan Walker
6/22/2009 05:13:56 PM
DIRECTOR

Memorandum re: Difference of Opinion between OGD and DDDP

Date:	July 16, 2009
From:	Brenda S. Gierhart, M.D., Medical Officer Office of Generic Drugs (OGD)
Through:	Dena R. Hixon, M.D., Associate Director for Medical Affairs, OGD and Gary J. Buehler, Director, OGD
To:	Elizabeth Dickinson, J.D., Office of the Chief Counsel (OCC)
Subject:	Division of Dermatology and Dental Products (DDDP) Response to OGD Request for Consultation (DDDP Consult #1144) finalized in DFS on June 22, 2009
Drug Product:	Imiquimod Cream, 5%
Reference Listed Drug:	Aldara® (imiquimod) Cream, 5%; Graceway Pharmaceuticals, LLC, NDA 20-723 (approved 2/27/97)
Pending ANDAs:	1) 78-548; Nycomed US Inc. (formerly Altana Inc) 2) 78-837; Perrigo Israel 3) 91-044; Tolmar

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Table of Contents:

I. Executive Summary

Imiquimod is an immune response modifier that has been evaluated in several therapeutic areas for various indications. Thus, there are many imiquimod experts within the various Divisions of the Office of New Drugs (OND), including Oncology (HFD-150 was assigned to regulate the innovator imiquimod IND 30,432 when it was opened in 1987), Antiviral (HFD-530 approved the external genital wart indication in 1997), and Dermatology (HFD-540 currently regulates the innovator imiquimod active INDs 30,432, 49,464, 49,480 and 66,331 and NDAs 20-723 and 22-483).

On March 16, 2009, the Office of Generic Drugs (OGD) sought the opinion of the OND Division of Dermatology and Dental Products (DDDP; HFD-540) prior to posting individual product bioequivalence recommendations on the FDA Guidances (Drugs) webpage for generic versions of Imiquimod Cream, 5% (reference listed drug, Aldara® Cream, 5%). The OGD Request for Consultation included a 1-page form, a 5-page OGD memorandum providing the background and discussion of the current issues regarding generic Imiquimod Cream, and a 5-page Draft Guidance on Imiquimod (Cream; Topical). The OGD specifically requested comments from the DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses (AK) (emphasis added). The OGD Request for Consultation also stated that the pending application ANDA 78-548 for a generic version of Imiquimod Cream, 5% is acceptable for approval from a regulatory and CMC perspective, and the OGD requested DDDP comments on the recommendations before taking an action on this application or posting the recommendations on the FDA webpage.

On June 22, 2009, the DDDP finalized their Response to the OGD Request for Consultation in a 5-page Memorandum. The DDDP did not list the OGD Draft Guidance on Imiquimod in their section entitled “Materials Evaluated”. No comments were provided by the DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses. Instead, the DDDP recommended a significant change from the past five years of advice provided to sponsors by the OGD, namely to conduct the Imiquimod Cream clinical endpoint bioequivalence study in the treatment of Superficial Basal Cell Carcinoma (sBCC). The DDDP provided their opinions without the support of data or references from the scientific literature. The DDDP appears to concur with the OGD that the Imiquimod Cream clinical endpoint bioequivalence study should not be in the treatment of external genital warts.

Due to the remaining difference of opinion between the OGD and DDDP, this memorandum has been written to explain the OGD's rationale for their continued recommendation to conduct the Imiquimod Cream clinical endpoint bioequivalence study in the treatment of AK. This document first summarizes the development of topical Imiquimod Cream and the related topical 5-Fluorouracil (5-FU) Cream. The opinions and comments provided by the DDDP in their Response to the OGD Request for Consultation are then individually addressed. The conclusion of the OGD is that insufficient justification was provided by the DDDP to support changing the advice previously given by the OGD to sponsors of topical Imiquimod, which has been summarized in the OGD proposed Draft Guidance on Imiquimod (Cream/Topical). It is recommended that OGD post the attached Draft Guidance on Imiquimod (Cream/Topical) and complete the review and potential approval of the pending Imiquimod Cream ANDAs.

II. Background-Topical Imiquimod

Imiquimod (code names R-837 and S-26308) is an immune response modifier currently available as a 5% topical cream [i.e., Aldara® (imiquimod) Cream, 5%; reference listed drug (RLD)]. The mechanism of action of imiquimod is unknown; however, it has been reported to stimulate local production of proinflammatory cytokines, such as interferon alpha (IFN-α), tumor necrosis factor alpha (TNF -α) and interleukin 6 (IL-6), resulting in stimulation of the immune system.

On July 31, 1987, the first IND for Imiquimod (IND 30,432) was opened with DORDP [Division of Oncology and Radiopharmaceutical Drug Products (HFD-150)] and later transferred to DAVP [Division of Antiviral Products (HFD-530)]. After the approval of the external genital wart indication in 1997, IND 30,432 was transferred (per DARRTS on 5/2/97) to the DDDP [Division of Dermatology and Dental Products (HFD-540)]. The original sponsor for the imiquimod RLD (i.e., the innovator) was 3M Pharmaceuticals. On December 29, 2006, Graceway Pharmaceuticals acquired 3M's branded pharmaceutical business (including Aldara® Cream) in the United States, Puerto Rico, Canada and Latin America.[1] Imiquimod clinical trials have been conducted or proposed by the innovator's two sponsors under (b) (4) different INDs or pIND, of which 4 are currently active (see Appendix; Table 6). The current innovator sponsor, Graceway Pharmaceuticals, has been evaluating lower doses of Imiquimod Cream (i.e., 2.5% and 3.75%) and the use of different excipients for their three approved indications. The current innovator sponsor anticipates that lowering the dose of Imiquimod Cream will permit daily dosing and significantly shorter treatment durations.

On February 27, 1997, Original NDA 20-723 for Aldara® (imiquimod) Cream, 5% was approved for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older by the Division of Antiviral Products (DAP). The U.S. was the first country in which Aldara® Cream received marketing approval.[2] Per the approved labeling, Aldara® Cream has minimal systemic absorption, dose proportionality was not observed, and it appears that systemic absorption is more dependent on the surface area of application than the amount of applied cream. Aldara® Cream is supplied as single-use packets, each of which contains 250 mg of the cream equivalent to 12.5 mg of imiquimod, in boxes containing either 12 or 24 packets each. NDA 20-723 was later transferred from the DAP to the DDDP.

[1] IND 30,432 Serial No. 265 (YY) letter date 10/26/07 "2007 Annual Report" pg. 3 of 21.
[2] IND 30,432 Serial No. 258 (YY) letter date 10/25/06 "2006 Annual Report" pg. 93.

On March 2, 2004, the DDDP approved supplement #015 (SE1-015; efficacy supplement for new or modified indication) for the new indication "for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratosis on the face or scalp in immunocompetent adults". The approval letter noted that the sponsor made three postmarketing study commitments as follows:

1. Conduct a phototoxicity study which includes the light absorption spectra from 280 to 320 nm and submit Final Report by March, 2006.
2. Conduct a study of the safety and efficacy of topical imiquimod in the treatment of actinic keratoses at other locations than the face or scalp, e.g. the extremities and submit Final Report by August, 2007.
3. Conduct a study of the short-term (up to 16 weeks) and longer term (for at least 1 year with 2 or more separate treatment applications to the same treatment area) safety of treating contiguous and non-contiguous surface areas larger than 25 cm^2 with numbers of patients as per ICH E1A and submit Final Report by December, 2007. The maximum amount of drug and surface area studied should be guided by limitations posed by available systemic bioavailability and safety information. The areas treated in such a study should include face and scalp, but should also include other locations (e.g. extremities as per commitment #2 above). Pharmacokinetic data to be obtained from a subset of at least 12 evaluable patients with maximal exposure from clinical studies above.

On July 14, 2004, the DDDP approved supplement #016 (SE1-016; efficacy supplement for new or modified indication) for the new indication "for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured". The approval letter noted that the sponsor made one postmarketing study commitment as follows:

1. Submit the follow-up data from the 5-year sBCC recurrence study 1412-IMIQ through completion of the study in the form of interim reports on September 30 each year beginning in 2005 and submit the Final Report by September 30, 2007.

On March 22, 2007, the DDDP determined that efficacy with Aldara was <u>not</u> demonstrated for the treatment of molluscum contagiosum in children aged 2-12 years (n=702) enrolled in two Phase 3, randomized, vehicle-controlled, double-blind studies (1494-IMIQ and 1495-IMIQ) and the DDDP approved supplement #020 (SE8-020; efficacy supplement with clinical data to support labeling claim) to insert new pediatric safety information regarding these failed molluscum contagiosum studies into the Aldara product labeling. The molluscum contagiosum pediatric studies were conducted according to the terms of the Written Request originally issued on December 28, 2001 and Pediatric Exclusivity was granted by the Agency on December 13, 2006.

On December 19, 2008, the 505(b)(1) NDA 22-483 for TRADENAME (imiquimod) Cream, 3.75% was submitted by Graceway Pharmaceuticals to the DDDP for the "treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults". Per the sponsor's NDA 22-483 cover letter, the 3.75% imiquimod formulation was developed to provide effective and well-tolerated treatment when dosed daily for a shorter duration and over a larger area (i.e., full face or balding scalp) than that approved for Aldara. Per the submitted labeling, imiquimod cream, 3.75% would be applied daily to the skin of the affected area (either the face or balding scalp) for two 2-week treatment cycles separated by a 2-week no treatment period. The cover letter also stated that the sponsor will be providing a new Tradename for the 3.75% formulation; however, the new Tradename has not yet been submitted. NDA 22-483 is currently under review.

Per the Verispan Physician Drug and Diagnosis Audit (PDDA), the most common projected use for Aldara® by patients aged 17 years and above as prescribed in U.S. office-based practices during 2005-2007 was diagnostic code 0781: Viral Warts (share (b) (4)%; (b) (4) uses) with the second being 7020: Actinic Keratosis (share (b) (4)%; (b) (4) uses) and the third being 1739: Malig Neo Skin NOS (share (b) (4)%; (b) (4) uses).[3] Per the same audit in patients aged 0-16, the most common projected use for Aldara was diagnostic code 0781: Viral Warts (share (b) (4)%; (b) (4) uses) Thus, the overwhelmingly most common projected use of Aldara in all age groups was Viral Warts.

Per the Aldara® (imiquimod) Cream, 5% approved product labeling, the dosing regimens differ for the three indications as follows:

- External genital warts: 3 times per week until total clearance or for a maximum of 16 weeks (i.e., maximum 48 applications); prior to normal sleeping hours, apply as a thin layer to wart area, rub in until the cream is no longer visible and leave on the skin for 6 - 10 hours, after which time the cream should be removed by washing the area with mild soap and water. The application site should not be occluded.
- Actinic keratosis: 2 times per week for 16 weeks (i.e., 32 applications); prior to normal sleeping hours, apply to a defined contiguous treatment area of approximately 25 cm^2 on the face (e.g., forehead and one cheek) or on the scalp (but not both concurrently) and leave on for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.
- Superficial basal cell carcinoma: 5 times per week for 6 weeks (i.e., 30 applications); prior to normal sleeping hours, apply sufficient cream to cover the treatment area and approximately 1 centimeter of skin surrounding the tumor, rub in until the cream is no longer visible and leave on for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.

While sBCC had the shortest recommended treatment duration (6 weeks) and the fewest number of applications (n=30), the complete response rate was not determined until 12 weeks post-treatment (i.e., study duration 18 weeks). AK had a similar number of applications (n=32) during

[3] Per NDA 20-723 Aldara® (imiquimod) Cream BPCA Drug Use Review by K Worthy, Pharm D/Division of Epidemiology/OSE/CDER finalized in DFS on 8/7/08 [**NOTE**: This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.]

a longer treatment duration (16 weeks); however, the complete response rate was determined at 8 weeks post-treatment (i.e., study duration 24 weeks). External genital warts had the highest number of possible applications (n=48) over a maximal 16 week treatment duration and the recurrence rate was determined at 12 weeks post-treatment (i.e., study duration 28 weeks).

Per the Medical Officer NDA 20-723 Reviews available in the Agency Division File System (DFS) and the one Medical Officer NDA 20-723 review available to the public at: http://www.fda.gov/cder/foi/nda/2004/020723_S016_ALDARA_CREAM.pdf and per the Aldara® (imiquimod) Cream, 5% approved product labeling, the Phase 3 clinical trials conducted for each of the three approved indications are as follows:

- External Genital Warts (EGW):
  - In a Phase 3, randomized, double-blind, vehicle-controlled clinical study (1004-IMIQ) conducted in the U.S. and Canada, 209 otherwise healthy subjects 18 years of age and older with genital/perianal warts were treated with Aldara Cream 5% or vehicle control 3 times per week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). The primary efficacy endpoint was the number of patients with complete clearance of baseline/target warts during treatment (maximum 16 weeks). Patients with a complete clearance of warts were followed for an additional 12 weeks to assess the recurrence rates. Of the 109 subjects treated with Aldara Cream 5%, 54 (50%) had a complete clearance of warts [with 11% (6/54) recurring during follow-up], 36 (33%) did not have a complete clearance of warts and 19 (17%) withdrew. Of the 100 subjects treated with vehicle, 11 (11%) had a complete clearance of warts [with 9% (1/11) recurring during follow-up], 62 (62%) did not have a complete clearance of warts and 27 (27%) withdrew. The median time to complete wart clearance was 10 weeks. During the treatment period, 28% (31/109) of subjects treated with Aldara Cream 5% developed new warts compared to 38% (38/100) in the vehicle group. It was noted in the primary Medical Review that since patients were allowed to be sexually active during the clinical trial, recurrence of treated genital warts and development of new warts may represent re-infection rather than inadequate treatment or expression of subclinical disease.
  - (b) (4) and will not be summarized.
- Actinic Keratosis (AK):
  - In two Phase 3, randomized, double-blind, vehicle-controlled, parallel group clinical studies (1444-IMIQ and 1446-IMIQ) conducted in the US and Canada, a total of 436 subjects with AK were randomized to treatment with either Aldara Cream or vehicle cream 2 times per week for 16 weeks. The primary efficacy endpoint was the "complete clearance rate" defined as the proportion of subjects at the 8-week post-treatment visit with no (i.e., zero) clinically visible actinic keratosis in the treatment area. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, and nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on either the face or scalp. The 25 cm^2 contiguous treatment area could be of any dimensions e.g., 5 cm by 5 cm, 3 cm by 8.3 cm, or 2 cm by 12.5 cm. It should be noted that sub-clinical AK lesions may become apparent in the treatment area during treatment with Aldara Cream. During the course of treatment, 48% (103/215) of subjects experienced an increase in AK lesions relative to the number present at baseline within the treatment area. Subjects with an increase in AK lesions had a similar response to those with no increase in AK lesions.

Table 1: Studies 1444-IMIQ and 1446-IMIQ AK Complete Clearance Rates (100% AK Lesions Cleared at 8-week Post-treatment Visit)

Study	Aldara Cream	Vehicle
1444-IMIQ	46% (49/107)	3% (3/110)
1446-IMIQ	44% (48/108)	4% (4/111)

Table 2: Studies 1444-IMIQ and 1446-IMIQ AK Partial and Complete Clearance Rates (75% or More Baseline AK Lesions Cleared at 8-week Post-treatment Visit)

Study	Aldara Cream	Vehicle
1444-IMIQ	60% (64/107)	10% (11/110)
1446-IMIQ	58% (63/108)	14% (15/111)

- In a Phase 3, double-blind, vehicle-controlled, 2:1 randomized study (1516-IMIQ), 270 subjects with AK on the upper extremities were randomized to treatment with either Aldara Cream (n=182) or vehicle cream (n=88) 2 times per week for 16 weeks. This study was conducted to address NDA 20-723 S-015 post-marketing commitment #2, which read "Conduct a study of the safety and efficacy of topical imiquimod in the treatment of actinic keratoses at other locations than the face or scalp, e.g. the extremities." The studies enrolled subjects with 4 to 8 AK lesions within a 25 cm^2 contiguous treatment area on the dorsal aspect of the forearm or hand (not both). Efficacy was determined at the 8-week post-treatment visit. The reviewing Medical Officer concluded that:

  > Aldara was superior to vehicle in the treatment of AK on the upper extremities, as assessed by the complete clearance rate. For both treatment groups, complete clearance rates were higher for the forearm than on the hand. Complete clearance rates for the upper extremities were lower than those seen in the trials conducted in which the treatment areas were the face or scalp (i.e., the approved indication). However, the upper extremities have been reported to be more treatment resistant.

Table 3: Study 1516-IMIQ AK Complete Clearance Rates (100% AK Lesions Cleared)

8-week Post-treatment Visit Outcome	Aldara Cream n=182	Vehicle N=88
Complete Clearance	45 (25%)	12 (14%)
Not Complete Clearance	127 (70%)	72 (82%)
8-week Post-treatment Count not done	10 (5%)	4 (5%)

- Superficial Basal Cell Carcinoma (sBCC):
  - In two Phase 3, double-blind, vehicle-controlled, parallel group, randomized clinical studies (1393-IMIQ and 1408-IMIQ) conducted in the U.S., a single primary sBCC in a total of 364 subjects was treated with Aldara Cream or vehicle cream 5 times per week for 6 weeks. Target tumors were biopsy-confirmed sBCC and had a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm (4.0 cm^2). Target tumors were not to be located within 1.0 cm of the hairline, or on the anogenital area or on the hands or feet, or to have any atypical features. The primary efficacy variable was the complete response rate determined at the 12-week post-treatment visit (i.e., 12 weeks after the last scheduled application of study cream) by clinical (visual) assessment of BCC and histological

evaluation of BCC (i.e., entire target tumor was excised and sent for histological examination for the presence of tumor). A complete responder was defined as a subject with:

a) No clinical (visual) evidence of BCC and no histological evidence of BCC at the target tumor site; or
b) Clinical (visual) evidence suspicious for BCC, but no histological evidence of BCC at the target tumor site, and the histological findings provided an explanation of the clinical assessment.

Table 4: Studies 1393-IMIQ and 1408-IMIQ Composite Clearance Rates at 12 weeks post-treatment for sBCC (defined as both clinical and histological clearance)

Study	Aldara Cream	Vehicle
1393-IMIQ	70% (66/94)	2% (2/89)
1408-IMIQ	80% (73/91)	1% (1/90)
Total	75% (139/185)	2% (3/179)

- In an open-label, uncontrolled, Phase 3, long-term (5-year) efficacy study (1412-IMIQ) conducted in Europe, Aldara Cream was applied once daily 5 days per week for 6 weeks in 182 enrolled subjects. Study was initiated on February 21, 2001. Target tumor inclusion criteria were the same as for the studies described above. At the 12-week post-treatment visit, subjects were clinically evaluated for evidence of persistent sBCC (no histological assessment) as the primary variable. Subjects with no clinical evidence of sBCC at the 12-week post-treatment visit entered the long-term follow-up period. At the 12-week post-treatment assessment, 90% (163/182) of the subjects enrolled had no clinical evidence of sBCC at their target site and 162 subjects entered the long-term follow-up period for up to 5 years. Limited follow-up data are available from this study and are presented in the table below:

Table 5: Study 1412-IMIQ Estimated Clinical Clearance Rates for sBCC

Follow-up Period				
Follow-up visit after 12- week post-treatment assessment	**No. of Subjects who remained clinically clear**	**No. of Subjects with sBCC recurrence**	**No. of Subjects who discontinued at this visit with no sBCC (a)**	**Estimated Rate of Subjects who Clinically Cleared and remained Clear (b)**
Month 3	153	4	5	87.4%
Month 6	149	4	0	85.1%
Month 12	143	2	4	83.9%
Month 24	139	4	0	81.6%
Month 36	135	2	2	81.6%
Month 48	129	3	3	79.3%

Source: Per approved Aldara PI labeling, IND 30,432 Annual Report Serial No. 258 (letter date October 25, 2006) Appendix III page 67 and IND 30,432 Annual Report Serial No. 265 (letter date October 26, 2007) Appendix III page 35 [**NOTE**: 6 deaths have occurred during the follow-up period]

b) Reasons for discontinuation included death, non-compliance, entry criteria violations, personal reasons, and treatment for nearby sBCC tumor.

c) Estimated rate of subjects who clinically cleared and remained clear are estimated based on the time to event analysis employing the life table method beginning with the rate of clinical clearance at 12 weeks post-treatment

- In an open-label, uncontrolled, Phase 3, long-term (5-year) efficacy study (1413-IMIQ) conducted in Australia and New Zealand, Aldara Cream was applied once daily for 7 days per week for 6 weeks in 169 enrolled subjects. Due to evaluating a different dosing regimen, this study will not be summarized

Aldara® (imiquimod) Cream, 5% is the reference listed drug (RLD) and there is no unexpired exclusivity for this product (i.e., Exclusivity code 1-433 for superficial basal cell carcinoma indication expired on July 14, 2007, Exclusivity code PED for pediatric exclusivity expired on September 2, 2007 and Exclusivity code PED for pediatric exclusivity expired on January 14, 2008). Two unexpired patents are listed for this product in the Orange Book Database as follows:

1) Method of Use Patent #4689338 for "treatment of genital warts" was to expire on August 25, 2009; however, this patent was extended 6 months due to sponsor successfully completing a Pediatric Written Request; now this patent (i.e., 4689338*PED) will expire on February 25, 2010.
2) Formulation Patent #5238944 was to expire on August 24, 2010; however, this patent was extended 6 months due to sponsor successfully completing a Pediatric Written request; now this patent (i.e., 5238944*PED) will expire on February 24, 2011.

Three firms ((b) (4) for ANDA (b) (4), Nycomed for ANDA 78-548, and Perrigo for ANDA 78-837) have filed a Paragraph IV Certification for Patent #5238944 as being invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. One firm (Tolmar Inc for ANDA 91-044) filed a Paragraph III Certification for Patents #4689338, 4689338-PED, 5238944, and 5238944-PED that stated these patents will expire on February 24, 2011 and that the firm does not intend to market their generic Imiquimod Cream prior to expiry.

To date, no ANDAs have been approved for Aldara® (imiquimod) Cream, 5% and thus, there are no Therapeutics Equivalents. Seventeen (17) Controlled Correspondences (see Appendix; Table 7), four (4) protocols (see Appendix; Table 8) and four (4) ANDAs (see Appendix; Table 9) have been submitted to the OGD for Imiquimod Cream, 5%.

III. Background: Topical 5-Fluorouracil

Several issues regarding the development of a generic topical 5-Fluorouracil (Efudex) 5% cream are relevant to the development of a generic topical Imiquimod Cream, 5%. Specifically, the OGD applied the general framework used for establishing bioequivalence in the development of a generic 5-Fluorouracil (5-FU) 5% cream (by Spear Pharmaceuticals) to the development of a generic Imiquimod Cream, 5%. It should also be noted that the approach to development of Spear's generic 5-FU 5% cream was upheld in the Agency's response to Citizen Petition 2004P-0557/CP1 submitted by Valeant Pharmaceuticals International, sponsor of Efudex® (5-FU) 5% cream.

Topical 5-FU 5% cream is an antineoplastic, antimetabolite in a vanishing cream base that is currently approved for the topical treatment of multiple actinic (i.e., solar) keratoses and superficial basal cell carcinomas (sBCC). On July 29, 1970, Efudex Cream, 5% and Solution,

2% and 5% were first approved under NDA 16-831 for the topical treatment of multiple actinic (or solar) keratosis based upon:

- expert testimony from six dermatologists
- three open label clinical studies (one study for each formulation):
  - 295 cases treated with 2% 5-FU solution; 78% with a "complete clinical response"
  - 215 cases treated with 5% 5-FU solution; 86% with a "complete clinical response"
  - 197 cases treated with 5% 5-FU cream; 84% with a "complete clinical response"
- controlled studies cross-referenced from NDA 16-765 [63 patients treated with a lower concentration of 1% 5-FU solution][4,5]

The sponsor of the Original NDA 16-831 was Hoffman-La Roche, Inc.

In 1976, Efudex Cream, 5% and Solution, 5% were approved under NDA 16-831 for the topical treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites based upon a study of 113 sBCC lesions in 54 patients, which demonstrated a 93% complete clearance rate.[6] Regarding superficial basal cell carcinomas, the **INDICATIONS AND USAGE** section of the approved labeling further states:

> The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%.

Per the Verispan Physician Drug and Diagnosis Audit (PDDA), the most common diagnosis associated with a mention of topical 5-FU by U.S. Office based physicians from 2002-2007 was diagnostic code 7020: actinic keratosis (2002=(b) (4); 2033=(b) (4); 2004=(b) (4); 2005=(b) (4) 2006=(b) (4) 2007=(b) (4)) and only a small percentage were diagnostic code 1739: Malig Neo Skin NOS (2002=(b) (4); 2033(b) (4); 2004=(b) (4); 2005=(b) (4); 2006=(b) (4); 2007=(b) (4)).[7]

Although the FDCA does not require clinical studies for the approval of generic drugs, it has been FDA's policy to require a clinical study to demonstrate bioequivalence for topical drugs, such as Efudex Cream, 5%, for which there is no suitable pharmacokinetic or pharmacodynamic endpoint, i.e., the amount of active ingredient of the drug cannot be measured in the blood or urine. On June 14, 1999, Spear Pharmaceuticals submitted to the OGD a meeting request and

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[4] Hon-Sum Ko, M.D., Medical Officer. Memorandum re: Consult 129 (DDDDP#994479) received 11/4/99 from HFD-600 (Mary Fanning, M.D.). Finalized November 19, 1999 by Jonathan K. Wilkin, M.D., Division Director, Division of Dermatologic and Dental Drug Products.

[5] John B. Sanders, M.D., Medical Officer. NDA 16-831 Summary of Basis of Approval dated June 4, 1970 on pg. 2-3 of 3 [submitted on December 21, 2004 by Valeant Pharmaceuticals International in Citizen Petition FDA-2004-P-0338 (formerly 2004P-0557) as Appendix 6].

[6] Gross, Kenneth et al. 5% 5-Fluorouracil cream for the treatment of small superficial basal cell carcinoma: efficacy, tolerability, cosmetic outcome, and patient satisfaction. *Dermatol Surg*. 2007 Apr; 33(4): 433-9.

[7] Per NDA 16-831 topical Efudex® (5-fluorouracil) Post-Marketing Analysis of All Adverse Events Review by Marilyn R. Pitts, Pharm. D., Safety Evaluation, Division of Adverse Event Analysis I (DAEA I) finalized in DFS on 3/28/08 [**NOTE**: This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.]

Protocol 99-022: a clinical endpoint, double-blind, 1:1 randomized, balanced, two-treatment, parallel study to evaluate the bioequivalence of 5-FU (5-FU) 5% topical cream versus Efudex® 5% cream in 180 men and women aged 35-85 years with at least 8 actinic keratosis (AK) lesions total on the forehead and temples. Spear did not propose including a placebo arm. In a regulatory letter dated December 10, 1999, the OGD recommended conducting the study with a placebo arm since actinic keratoses lesions are reported to undergo spontaneous regression. Spear incorporated a placebo group in the study. Spear did not propose evaluating subjects with superficial basal cell carcinoma (sBCC). The OGD did not require Spear to conduct a clinical trial for the sBCC indication.

On December 22, 2004, Spear submitted an ANDA for a generic version of 5-FU. On December 21, 2004, the current sponsor for Efudex Cream, 5% (Valeant Pharmaceuticals International) submitted Citizen Petition 2004P-0557/CP1 requesting that FDA refrain from approving a generic version of Efudex until the generic applicant had conducted a clinical trial to demonstrate bioequivalence for sBCC. In responding to the citizen petition, the DDDP disagreed with the OGD. The DDDP recommended that clinical trials should be conducted in both AK and sBCC. The OGD concluded:

> "There is reasonable scientific evidence that equivalent performance in a clinical endpoint study in AK will also predict equivalent delivery of the drug substance to the site of action for sBCC in the adjoining cell layer. Therefore, there is not a substantial risk that a generic 5-FU cream product showing equivalence in a study of AK would result in a clinical disadvantage compared to the RLD when used in the treatment of sBCC when conventional methods of surgical excision are impractical."[8]

Because the DDDP disagreed with the OGD on this issue, Dr. Julie Beitz (Director of ODE III, of which the DDDP is a component) was asked to review the matter. In her memorandum dated December 3, 2007, Dr. Beitz agreed with the OGD that a study in AK would be sufficient to establish bioequivalence for both AK and sBCC for 5-FU 5% cream. Dr. Beitz cited numerous reasons for her conclusion, including: (1) Efudex itself has previously been shown to be safe and effective for the treatment of both AK and sBCC; (2) "[t]he published literature supports the contention that the extent of skin involvement, and thereby the sites of action, for AK and sBCC are the same (i.e., the epidermis and the upper dermis)"; (3) "[t]he stratum corneum is the predominant barrier to topical drug delivery for both the epidermis and upper dermis"; (4) "[e]rosion or compromise of the skin in sBCC can result in greater drug exposure than in AK, which typically involves a thickened stratum corneum"; (5) because Efudex 5% cream and 5% solution are both approved for treating AK and sBCC,"[t]his argues against some critical formulation issue that could meaningfully affect the ability of these topical 5-FU products to deliver drug to the site of action for the approved uses"; (6) Spear's 5-FU cream formulation produced complete clearing of lesions in AK patients comparable to Efudex in a randomized, placebo-controlled clinical trial; (7) Spear's 5-FU cream formulation contains the same active ingredient in the same amount and dosage form as the reference product and Spear's AK study demonstrated that the two products perform the same despite differences in formulation; and (8) "[g]iven the 88% clearance rate for the reference product, it is reasonable to expect that any

[8] Dena R. Hixon, MD Associate Director for Medical Affairs, Office of Generic Drugs; Consultation Response Memorandum finalized on 2/20/07 (pg. 16 of 21).

material differences in depth of penetration of the Spear would have been seen as a lower complete clearance rate for the Spear formulation".[9] Dr. Beitz concluded that neither AK or sBCC was particularly "difficult to treat," and rejected Valeant's argument in its citizen petition that a bioequivalence study needed to be done in sBCC as the more "difficult to treat" condition.[6]

On April 11, 2008, FDA denied Valeant's citizen petition and approved Spear's ANDA for generic 5-FU. On April 25, 2008, Valeant sued FDA, alleging that FDA's actions in approving Spear's ANDA and denying its citizen petition were arbitrary and capricious, and sought a temporary restraining order (TRO) to enjoin FDA's approval of Spear's ANDA. On April 30, 2008, FDA sought a stay in the TRO proceedings to determine appropriate administration steps relating to Dr. Jonathan Wilkin's 2-page opinion letter submitted by Spear on March 14, 2007. The issue was that although Dr. Beitz knew Dr. Wilkin's opinion, prepared after he left FDA as the Division Director of the DDDP, Dr. Beitz was not aware until after FDA approved Spear's ANDA that Dr. Wilkin had initialed consult memoranda regarding testing protocols for Spear's generic 5-FU product application while he had worked at FDA. The Court granted a stay on May 1, 2008. During the pendency of that stay, Spear agreed to stop marketing its product.

FDA then undertook a formal administrative reconsideration of Spear's ANDA to address two additional scientific issues that it did not identify until after approval: whether Spear should have been required to submit pharmacokinetic data for approval, and whether additional or different clinical efficacy data should have been submitted. Dr. Douglas Throckmorton, M.D., the Deputy Director of CDER, wrote the agency's reconsideration memorandum. Dr. Throckmorton concluded that no additional data was needed for approval of Spear's application, based largely on the studies that Spear had already conducted and the nature of the active ingredient, 5-FU. As part of the agency's reconsideration of Spear's application, FDA addressed Dr. Wilkin's potential conflict of interest by, among other things, asking Dr. Beitz to "evaluate whether [she] would have reached the same conclusion as stated in [her] December 3, 2007 decision, even if Dr. Wilkin had not made his March 14, 2007 submission in support of Spear's ANDA." In her analysis, dated May 29, 2008, Dr. Beitz determined that the scientific information presented by Dr. Wilkin was independently supported by references in the record, including references that had previously been submitted to FDA and that she had independently found. Dr. Beitz "unequivocally state[d] that [she] would have reached the same conclusion regarding the approvability of Spear's ANDA even if [she] had not considered Dr. Wilkin's submission."[10]

On July 20, 2009, a hearing is scheduled in the United States District Court, Central District of California, Southern Division regarding Valeant's suit, Case No. SACV 08-0449 AG (AGRx). In preparation for this hearing, FDA filed on June 8, 2009 a "[Proposed] Statement of Uncontroverted Facts and Conclusion of Law" and a "Federal Defendants' Memorandum on Points and Authorities in Support of Motion for Summary Judgment", Spear Pharmaceuticals, Inc. filed a Motion for Summary Judgment as Intervenor Defendant, and Valeant Pharmaceuticals International filed a "Plaintiff Valeant Pharmaceutical International's Rule 56-1 Statement of Uncontroverted Facts and Conclusion of Law" and a "Valeant Pharmaceuticals

[9] Julie Beitz, MD, Director, Office of Drug Evaluation III, OND. Memorandum; Subject: Valeant Pharmaceuticals International Citizen Petition 2004P-0557; finalized in DFS on 12/14/07.
[10] Julie Beitz, MD, Director, Office of Drug Evaluation III, OND. Memorandum; Subject: Valeant Pharmaceuticals International Citizen Petition 2004P-0557; finalized in DFS on 5/29/08.

International's Notice of Motion and Motion for Summary Judgment: Memorandum of Points and Authorities in Support; Rule 56-1 Statement of Uncontroverted Facts and Conclusions of Law; and [Proposed] Judgment. Several of the facts contained in the FDA documents have been included in the discussion of topical 5-FU.

IV. Review of DDDP's Response to OGD Request for Consultation

On March 16, 2009, the OGD sought the opinion of the OND Division of Dermatology and Dental Products (DDDP) prior to posting individual product bioequivalence recommendations on the FDA Guidances (Drugs) webpage at:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

for generic versions of Imiquimod Cream, 5% [reference listed drug, Aldara® (imiquimod) Cream, 5%]. The OGD Request for Consultation included a 1-page form, a 5-page OGD memorandum providing the background and current issues regarding generic Imiquimod Cream, and a 5-page Draft Guidance on Imiquimod (Cream; Topical). The OGD specifically requested comments from the DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses (AK) (emphasis added). The OGD Request for Consultation stated that the OGD had provided recommendations to a number of generic sponsors in response to controlled correspondences for a clinical endpoint bioequivalence study in the treatment of AK. Currently, the OGD has three pending applications (ANDA 78-548, ANDA 78-837, and ANDA 91-044) for a generic version of Imiquimod Cream and each of these ANDAs contains a clinical endpoint bioequivalence study conducted in the treatment of AK. The OGD Request for Consultation also stated that application ANDA 78-548 for a generic version of Imiquimod Cream, 5% is acceptable for approval from a regulatory and CMC perspective, and the OGD requested DDDP comments on the recommendations before taking an action on this application or posting the recommendations on the FDA webpage.

On June 22, 2009, the DDDP finalized their Response to the OGD Request for Consultation in a 5-page Memorandum. The DDDP did not list the OGD Draft Guidance on Imiquimod in their section entitled "Materials Evaluated". Instead, the DDDP listed that the materials evaluated were the Aldara label (approval date 3/22/07), the Efudex label (approval date 10/13/05) and the Agency Response to Citizen Petition 2004P-0557/CP1 (submitted by Valeant Pharmaceuticals, manufacturer of Efudex). No comments were provided by the DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses or the 5-page Draft Guidance on Imiquimod. Instead, the DDDP recommended a significant change from the past five years of advice provided to sponsors by the OGD, namely to conduct the Imiquimod Cream clinical endpoint bioequivalence study in the treatment of Superficial Basal Cell Carcinoma (sBCC). The DDDP provided their opinions without the support of data or references from the scientific literature. The DDDP appears to concur with the OGD that the Imiquimod Cream clinical endpoint bioequivalence study should not be in the treatment of external genital warts.

The following individual opinions and comments provided in the DDDP Response to the OGD Request for Consultation (finalized in DFS on June 22, 2009) will now be addressed.

A. Topical Imiquimod's Site of Action
B. Topical Imiquimod's Limited AK Indication
C. Topical Imiquimod's Indication for External Genital Warts (EGW)
D. sBCC has Least Variability
E. sBCC has Shortest Duration of Treatment and Duration of Treatment is Same for All Patients
F. Two Primary Endpoints (i.e., Clinical and Histological) with sBCC versus One Primary Endpoint (i.e., Clinical) with AK
G. Success Rate Highest for sBCC
H. Assess BE by Most Stringent Outcome Criteria
I. Most Stringent Criteria is Most Sensitive in Discerning a Difference

A. Topical Imiquimod's Site of Action

DDDP Statement:

"For imiquimod, the shared sites of action for the three indications are the epidermis and papillary (upper) dermis, since all of the lesions are epidermal and can or do extend into the papillary dermis. However, actinic keratoses do not typically extend into the dermis." (pg. 2 of 5)

OGD Response:

The DDDP did not support their statement that actinic keratoses do not typically extend into the dermis with data or references from the scientific literature. If one accepts their statement at face value, it would only be pertinent if no actinic keratosis extended into the dermis, thereby resulting in two different sites of action for the AK and sBCC indications. However, the DDDP agrees with the OGD that the shared sites of action for the three Imiquimod indications are the epidermis and papillary (upper) dermis and all of the lesions are epidermal and can or do extend into the papillary dermis. As stated in the OGD Request for Consultation, "[w]hen the reference drug product is approved for more than one indication with the same site of pharmacologic activity, bioequivalence is generally established with a single study in the indication that is most likely to discern differences between the generic and reference products" (pg. 3). Since the site of action is shared for all three of Imiquimod's approved indications, the site of action can not be used to determine the most discriminatory treatment indication that should be used to establish bioequivalence between the generic and reference product.

B. Topical Imiquimod's Limited AK Indication

DDDP Statement:

"Imiquimod is specifically indicated for nonhyperkeratotic, nonhypertrophic AK (emphasis added), a sub-type of actinic keratosis to which 5-FU is not restricted. Topical 5-FU has the broader indication of "multiple actinic or solar keratosis," i.e., there is no restriction relating to hyperkeratosis (thickened stratus corneum)." (pg. 3 of 5)

OGD Response:

While it is a true statement that the AK indication for topical Imiquimod is limited and the AK indication for topical 5-FU is broader, the DDDP does not provide a rationale for why this fact should be a concern, particularly since the sBCC indication for topical Imiquimod is also limited and the sBCC indication for topical 5-FU is also broader. Given that the stratum corneum is the primary barrier to skin penetration, it would be reasonable to believe that it would be more

difficult for a drug to penetrate into a lesion with a thickened stratum corneum and perhaps less difficult for a drug to penetrate into a lesion with a compromised stratum corneum. If this is the argument and if the DDDP is recommending conducting the study in sBCC due to some sBCC lesions having a thickened stratus corneum (hyperkeratosis), the DDDP does not provide data or references from the scientific literature regarding how frequently sBCC lesions have areas of hyperkeratosis. Since the site of action is shared for all three of Imiquimod's approved indications, hyperkeratosis would need to be present in a high percentage of sBCC for this to be a factor to be used to determine the most discriminatory treatment indication that should be used to establish bioequivalence between the generic and reference product.

Regarding the sBCC indication for topical Imiquimod being limited and the sBCC indication for topical 5-FU being broader, the sBCC indication for topical Imiquimod is restricted to "biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured". Per the INDICATIONS AND USAGE section of the approved labeling for Efudex, the sBCC indication for topical 5-FU is broader, i.e.,

> "In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites…The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%".

Thus, the Efudex approved indication in sBCC does not stipulate a maximal tumor diameter, does not specify particular anatomical locations and does not limit treatment to immunocompetent adults.

It is the opinion of OGD that both the AK and sBCC Indications approved for topical imiquimod and topical 5-FU differ because 1) the Inclusion and Exclusion Criterion (i.e., the specific patient population enrolled) differed in the topical imiquimod and topical 5-FU pivotal clinical trials with the approved Indications reflecting these different populations, and 2) drug products approved in the far distance past (such as topical 5-FU, which was first approved in 1970) tend to have been granted broader indications that drug products approved in the recent past (such as topical imiquimod, which was first approved in 1997).

C. Topical Imiquimod's Indication for External Genital Warts (EGW)

DDDP Statement:

"Another factor which must be considered is that, unlike 5-FU, imiquimod is also indicated for external genital warts, a sexually-transmitted disease of viral etiology. We note too that prominent acanthosis (thickened epidermis) is an additional feature that sets this indication apart from AK and sBCC." (pg. 4 of 5)

OGD Response:

The DDDP notes that Imiquimod is effective in external genital warts with a prominent acanthosis (thickened epidermis) and this feature sets this indication apart from AK and sBCC. However, this difference does not support the use of either the treatment of AK or sBCC in clinical endpoint bioequivalence studies since neither is associated with prominent acanthosis. Since the site of action is shared for all three of Imiquimod's approved indications, the presence or absence of acanthosis alone can not be used to determine the most discriminatory treatment indication that should be used to establish bioequivalence between the generic and reference product.

D. sBCC has Least Variability

DDDP Statement:

"Of the three indications, sBCC would have the least variability in the disease state and expected disease course, since labeling limits treatment to one lesion with an upper limit diameter of 2.0 cm, and this sub-type of BCC has a relatively consistent clinical presentation. Additionally, sBCC is not generally reported to spontaneously remit (although it may). In the consultant's experience spontaneous remission is more likely/commonly seen with AK and EGW." (pg. 4 of 5)

OGD Response:

As stated in the OGD Request for Consultation, "[t]he most sensitive clinical endpoint bioequivalence study design is generally conducted in an indication with the least inherent variability, using the lowest recommended treatment dose and/or duration, and the earliest evaluation time at which a significant treatment effect is expected" (pg. 4). The DDDP considers sBCC to be a less variable disease than AK; however, no data or references from the scientific literature have been provided to support this statement. The significantly restricted nature of Imiquimod's approved indication in sBCC [i.e., "biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feed), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured"] is related to the specific Inclusion/Exclusion criteria for the individual clinical study. Since any Imiquimod clinical endpoint bioequivalence study conducted in patients with AK would have detailed and specific Inclusion/Exclusion criteria, it is reasonable to assume that the variability of the two disease states would be similar when evaluated in a clinical endpoint bioequivalence study. In addition, randomization and enrollment of sufficient subjects in each treatment arm and inclusion of a placebo arm as recommended should sufficiently control for any individual AK undergoing spontaneous remission.

It should be noted that the primary efficacy endpoint in the two innovator imiquimod pivotal studies had the greatest variability and the higher cure rate in the sBCC indication (i.e., composite clearance rate at 12 weeks for Aldara in Study sBCC1 was 70% and in Study sBCC2 was 80%) compared to the AK indication (i.e., complete clearance rates for Aldara in Study AK1 was 46% and in Study AK2 was 44%). In the innovator imiquimod external wart pivotal Study EGW1, a marked gender effect was demonstrated for the primary efficacy endpoint (i.e., complete clearance rate for Aldara was 33% in males compared to 72% in females). Thus, the OGD has recommended that the clinical endpoint bioequivalence study be conducted in the

treatment of AK due to the decreased variability in the primary efficacy endpoint and the lower cure rate in the pivotal studies conducted in the treatment of AK.

E. sBCC has Shortest Duration of Treatment and Duration of Treatment is Same for All Patients

DDDP Statement:

"At 6 weeks (30 doses total), the duration of treatment for which a significant treatment effect is expected is shortest for sBCC, and the duration of treatment is the same for all patients. We make a distinction between the duration of treatment (6 weeks) and the timepoint of efficacy assessment (12 weeks post-treatment): it is the 6 weeks of treatment that makes for the effect assessed at Week 18. The duration of treatment may be > twice as long for the EGW (up to 16 weeks; maximum of 48 doses) and AK (16 weeks; 32 doses) indications." (pg. 4-5 of 5)

OGD Response:

While the approved Aldara (imiquimod) Cream 5% labeling recommends the shortest treatment duration (6 weeks) and the fewest number of applications (n=30) for superficial basal cell carcinoma, the complete response rate was not determined until 12 weeks post-treatment. The labeling recommends a similar number of applications (n=32) administered over a longer treatment duration (16 weeks) for actinic keratoses; however, the complete response rate was determined more quickly (at 8 weeks post-treatment). External genital warts had the highest number of possible applications (n=48) over a maximal 16 week treatment duration and the recurrence rate was determined at 12 weeks post-treatment (i.e., study duration 28 weeks). Thus, the OGD concurs with the DDDP that the EGW indication is less likely to discern a difference between a generic product and the RLD in a clinical bioequivalence study due to the prolonged treatment duration, maximum of 48 doses and prolonged follow-up period. This reviewer sees little difference between the 30 doses of treatment recommended for sBCC and the 32 doses of treatment recommended for AK. The duration of the combined treatment and follow-up period for AK (i.e., 24 weeks) and sBCC (i.e., 18 weeks) are similar. It is also anticipated that AK subjects would be easier to enroll. Per the Verispan Physician Drug and Diagnosis Audit (PDDA), the projected use for Aldara® by patients aged 17 years and above as prescribed in U.S. office-based practices during 2005-2007 for diagnostic code 7020: Actinic Keratosis was share (b) (4)%; (b) (4) uses, while diagnostic dose 1739: Malig Neo Skin NOS was only share (b) (4)%; (b) (4) uses.

F. Two Primary Endpoints (i.e., Clinical and Histological) with sBCC versus One Primary Endpoint (i.e., Clinical) with AK

DDDP Statement:

"In a comparative clinical bioequivalence trial of imiquimod in the treatment of sBCC, drug delivery to the sites of action (epidermis and papillary dermis) would be assessed by both clinical and histological endpoints. Outcomes would be assessed only clinically for AK and EGW which might be relatively less sensitive measures of assessing treatment outcomes. That addition of histological assessment makes for a more sensitive measure than does clinical assessment alone is evidenced by the fact that 6% of Aldara-treated subjects "who appeared to be clinically clear

[11] Per NDA 20-723 Aldara® (imiquimod) Cream BPCA Drug Use Review by K Worthy, Pharm D/Division of Epidemiology/OSE/CDER finalized in DFS on 8/7/08 [**NOTE**: This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.]

had evidence of tumor on excision of the clinically-clear treatment area: (see Clinical Studies section of Aldara label)." (pg. 5 of 5)

OGD Response:
DDDP asserts that the most sensitive measure should be used. However, the OGD is seeking to evaluate the indication that would be most sensitive in discerning a difference between a generic product and the RLD in a clinical bioequivalence study. DDDP provides no data or references from scientific literature that the use of two primary endpoints would be more sensitive in discerning a difference between a generic product and the RLD than would one primary endpoint. In fact, the success of using two primary endpoints with sBCC in the innovator clinical trials resulted in higher success rates with sBCC than in AK (complete clearance rate for treatment minus complete clearance rate for vehicle was 73% for sBCC versus 42.5% for AK).[12] Thus, it may be harder to demonstrate a difference between a generic product and the RLD in the sBCC population. In addition, the actual definition of a complete responder in the pivotal sBCC trials was any subject with:

- No clinical (visual) evidence of BCC and no histological evidence of BCC at the target tumor site; OR
- Clinical (visual) evidence suspicious for BCC, but no histological evidence of BCC at the target tumor site, and the histological findings provided an explanation of the clinical assessment.

Thus, complete responders were required to have no histological evidence of BCC (with or without clinical evidence suspicious for BCC) which is in essence a single primary efficacy endpoint.

G. Success Rate Highest for sBCC
DDDP Statement:
"Although the success rates in the clinical trials supporting NDA approval for imiquimod in the treatment of sBCC were the highest of all three indications (see Aldara label), so too was the bar for establishing success, i.e., the composite endpoint of clinical and histological clearance." (pg. 5 of 5)

OGD Response:
See above response for "F". Clinical evidence of clearance was not required.

H. Assess BE by Most Stringent Outcome Criteria
DDDP Statement:
"If approval of a generic imiquimod product is to be based on study of one indication, we believe that public health would be best served were bioequivalence established in the indication which had the most stringent criteria for assessing outcomes." (pg. 5 of 5)

OGD Response:
The public health will be best served by evaluating Imiquimod Cream in the patient population most sensitive to discerning a difference between a generic product and the RLD. The DDDP has not provided evidence to support the superiority of the sBCC population over the AK population in discerning a difference between a generic Imiquimod Cream and the RLD.

[12] Per Tables 11 (AK) and 12(sBCC) in the CLINICAL STUDIES section of the Aldara approved labeling.

I. Most Stringent Criteria is Most Sensitive in Discerning a Difference

DDDP Statement:

"We believe the indication which had the most stringent criteria for assessing outcomes would be the most sensitive in discerning a difference between the generic product and the RLD. For imiquimod, we believe this indication to be superficial basal cell carcinoma." (pg. 5 of 5)

OGD Response:

See response to "H".

V. Conclusions

While the OGD respects the opinions of the DDDP, the OGD considers their opinions to be insufficient to change the advice given by the OGD to sponsors over the past five years for topical Imiquimod Cream.

VI. Recommendations

1) No changes are recommended to be made to the advice given by the OGD to sponsors during the past five years for topical Imiquimod Cream.
2) Recommend posting the Draft Guidance on Imiquimod (Cream/Topical).
3) Recommend completing the review and approval of the acceptable pending topical Imiquimod Cream ANDAs.

_____ _____

Brenda S. Gierhart, M.D. Date
Clinical Reviewer
Office of Generic Drugs

_____ _____

Dena R. Hixon, M.D. Date
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____

Gary Buehler Date
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

cc: OGD (HFD-600): G. Buehler/D. Conner/D. Hixon/B. Gierhart/D. Catterson
OCC: Elizabeth Dickenson, J.D.
DDDP (HFD-540): Susan Walker, M.D., Director/Jill Lindstrom, M.D., Team Leader/Brenda Carr, M.D.
ODE 3: Julie G. Beitz, M.D., Director/Maria R. Walsh, RN, MS, Regulatory Scientist

[**NOTE**: The therapeutic drug class for Imiquimod Cream 5% is "antiviral-other-systemic" (#7030190), which is assigned to OGD Bio Team 8; Innovator NDA 20-723 Aldara® is regulated by Division of Dermatology and Dental Products (DDDP; HFD-540)]

VII. Appendix

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Table 6: Imiquimod 5% Topical Cream (Code Name R-837) Innovator INDs (i.e., Graceway Pharmaceuticals, LLC or 3M Pharmaceuticals listed as Current Sponsor) n=15

IND Number	Indication	Date IND Received	Status	Current CDER Division
30,432	Antiviral in external genital/perianal warts	7/31/87	Active	DDDP (IND originally opened with DORDP, then transferred to DAVP and later to DDDP)
(b) (4)				
49,464	Basal cell carcinoma	12/21/95	Active	DDDP
49,480	Actinic keratosis	12/22/95	Active	DDDP
(b) (4)				
66,331	Treatment for pediatric molluscum contagiosum	12/6/02	Active	DDDP

Source: compiled by this reviewer from DARRTS search conducted on 6/29/09
DAVP=Division of Antiviral Products (HFD-530)
DDDP=Division of Dermatology and Dental Products (HFD-540)
DDOP=Division of Drug Oncology Products (HFD-150)
DORDP=Division of Oncology and Radiopharmaceutical Drug Products (HFD-150)
(b) (4)

Table 7: Imiquimod Cream, 5% Controlled Correspondences in OGD Database (n=17: 7 Closed, 10 Open)

CTL No.	Title	Description	Status	Doc Date	Due Date; Date Closed	From
04-381	Imiquimod Cream 5%	Request for guidance of clinical study (2-pg letter)	Closed	4/22/2004	7/3/04; 2/22/05	Teva
Summary 04-381: Teva stated conducting BE study in patients with warts would involve more difficult recruitment, longer treatment duration and result in greater patient exposure to the unapproved test drug product. Teva						

CTL No.	Title	Description	Status	Doc Date	Due Date; Date Closed	From
requested confirmation that conducting one clinical study in adults with actinic keratosis is sufficient to obtain approval for all Aldara Cream indications. OGD agreed with Teva and provided 12 comments in a regulatory letter dated 2/22/05 regarding the recommended study design for the single BE study in actinic keratosis patients, including applying treatment twice weekly for 16 weeks in all patients, enrolling patients with at least 4 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 continuous treatment area on face or scalp and evaluating proportion of patient with complete clearance of AK lesions at week 24 (i.e., 8 weeks after the end of treatment) as the primary endpoint.						
04-1043	Imiquimod Topical Cream	Requesting confirmation of proposed composition (2-pg fax)	Closed	10/21/2004	1/15/05; 3/24/05	(b) (4)
Summary 04-1043: (b) (4) provided a proposed composition of their generic version of Aldara cream and requested confirmation of the acceptability of the composition, which included the inactive (b) (4) (b) (4) OGD called firm on 3/24/05, concurred that the inactive (b) (4) at the level proposed was acceptable and noted that current IIG and COMIS incorrectly listed this inactive (b) (4) and it would be corrected (b) (4) No letter sent.						
04-1158	Imiquimod Topical Cream	Requesting what type of study would be required (1-pg letter)	Closed	12/2/2004	2/19/05; 2/16/05	(b) (4)
Summary 04-1158: (b) (4) requested BE requirements for topical Imiquimod Cream. OGD called firm on 2/16/05 and informed them to conduct a clinical endpoint study in patients with actinic keratosis. No letter sent.						
05-0341	Imiquimod Cream	Request for comparative dissolution method (1-pg letter)	Closed	3/14/2005	6/10/05; 8/17/05	Apotex
Summary 05-0341: Apotex requested copy of OGD/FDA dissolution test method for Aldara cream, to perform *in vitro* studies. OGD called firm on 8/17/05 to inform them that there are no specific methods for these products and firm should follow the recommendations in the SUPAC SS guidance as to how to conduct and develop the method for these semi-solid drug products. Firm also informed that *in vitro* testing was not required for topical drug products pre-approval. No letter sent.						
05-0677	Imiquimod	Requesting statement regarding whether IND is requested for BE study conducted with Imiquimod and whether Imiquimod is cytotoxic (1-pg fax)	Closed	6/1/2005	8/2/05; 8/29/05	(b) (4)
Summary 05-0677: The statements were requested due to the IRB for (b) (4) Medical Center in (b) (4) not allowing the investigators to begin an upcoming industry trial until the FDA provided the statements. OGD responded in the 8/29/05 regulatory letter that FDA does not consider Imiquimod to be cytotoxic. The letter also provided guidance for when a new IND would be required.						
05-0690	Imiquimod Cream	BE Protocol - Clinical Endpoint Study (2-pg letter)	Open	6/2/2005	8/7/05	Altana
Summary 05-0690: Altana requests confirmation that: 1) a single successful BE study in AK will be sufficient for approval of any Imiquimod Cream indications that are not protected by patent or exclusivity, 2) even if a Method of Use patent becomes listed for Aldara for AK (per Altana, a Method of Use patent is not yet listed by the Aldara NDA holder for AK), that this Method of Use patent listing will not delay approval of an Imiquimod Cream ANDA, and 3) the FDA response to the Citizen's Petition filed by Valeant Pharmaceuticals International for Efudex requesting requirement of a study in superficial basal cell carcinoma (sBCC) for approval of AK and sBCC will not delay approval of an Imiquimod Cream ANDA.						
05-0876	Imiquimod Cream Inactive Level	Controlled Correspondence of the proposed inactive level of oleic acid (1-pg fax dated 6/28/05, 4-pg fax dated 6/27/05, 3 scientific articles)	Open	6/28/2005	9/10/05	Altana
Summary 05-0876: Altana requests confirmation of the acceptability of their proposed inactive level of oleic acid (i.e., (b) (4) in Altana's Imiquimod Cream 5% and submitted 3 articles (81-pg, 14-pg and 8-pg) to support this level.						
06-0339	Imiquimod Cream	Bioequivalence Requirements (2-pg fax)	Open	3/6/2006	5/13/06	Apotex
Summary of 06-0339: Apotex submitted a summary (i.e., one-paragraph) of their proposed AK clinical endpoint BE study, which appears quite similar to the design of the Phase 3, pivotal Aldara AK studies, and asked 3 questions: 1) Is this a design that will be acceptable to FDA, 2) Is the complete clearance rate the appropriate primary efficacy measure? and 3) Are there other efficacy variables (secondary) required to be measured?						
06-	Imiquimod Cream	Requesting guidance (1-pg letter)	Open	4/11/2006	6/18/06	Perrigo

CTL No.	Title	Description	Status	Doc Date	Due Date; Date Closed	From
0522						
Summary of 06-0522: Perrigo requested guidance on the design of an *in vivo* bioequivalence study, and the requirements for *in vitro* dissolution testing for Imiquimod Cream 5%.						
06-0652	Imiquimod Cream	Bioequivalence Requirements (1-pg letter)	Open	5/2/2006	7/14/06	(b) (4)
Summary of 06-0652: (b) (4) requests that the Agency advise them on the BE requirements for submission of an ANDA for Imiquimod Cream 5% (AB rating).						
06-0707	Imiquimod Cream	Requesting testing requirements and bioequivalence recommendations (1-pg letter)	Open	5/11/2006	7/30/06	(b) (4)
Summary of 06-0707 (b) (4) requests the Agency testing requirements and the bioequivalence recommendations for an ANDA for Imiquimod Cream 5%.						
07-0219	(b) (4) Imiquimod Cream	Query	Open	1/23/2007	4/13/07	(b) (4)
Summary of 07-0219: (b) (4) provided the formula compositions of their Imiquimod Cream 5% (b) (4) (b) (4) They requested "inputs from OGD to understand if we are close to the composition disclosed by Innovator on these two products before initiating Clinical Efficacy trials which are very expensive".						
07-0220	Imiquimod Cream	BE Requirements (e-mail)	Open	2/2/2007	4/13/07	(b) (4)
Summary of 07-0220: (b) (4) sent an e-mail request to OGD Aaron Sigler that stated "I noticed that OGD has received an application for Imiquimod Cream, containing a paragraph IV certification. In light of this, I'm hoping that perhaps the agency has already responded to a Controlled Correspondence regarding the requirements for demonstration of bioequivalence for a generic, and that you could give me a quick read on whether a clinical endpoint study will be required using one indication or whether a study will be required for each indication. If the agency is only requiring a study using one indication, please let me know which indication should be used."						
08-0081	Imiquimod Cream	Requesting guidance regarding acceptability (1-pg fax)	Closed	12/10/2007	3/24/08; 3/27/08	Teva
Summary of 08-0081: Teva Pharmaceuticals USA provided two formulations being considered for an Imiquimod Cream, 5% formulation for filing an ANDA and requested guidance in determining if either of these formulations would be found acceptable for the submission of an original ANDA for Aldara Cream, 5%. In the 3/27/08 telephone call, OGD advised that either formulation would be acceptable if filed in an ANDA for Imiquimod Cream 5% and should they want to be more in line (Q1 and Q2 which is not required) with the RLD Aldara NDA 20-723, they should consider (b) (4) % for the (b) (4) and (b) (4) % for the (b) (4) as proposed in opposite formulations. In the OGD memo for this telephone call, it was noted that (b) (4) No letter was sent.						
08-0693	Imiquimod Cream alternative packaging	Request clarification on specific packaging of product (e-mail)	Closed	6/11/2008	8/11/08; 7/28/08	Nycomed
Summary of 08-0693: Amy M. Byrom, Manager, Regulatory Affairs, Nycomed, sent an e-mail request to OGD Martin Shimer that stated Nycomed has a pending ANDA for Imiquimod Cream 5% packaged in boxes of 12 single-use foilpacs, as supplied by the RLD, Aldara cream 5% and Nycomed is (b) (4) OGD called firm on 7/28/08 to respond that the proposed (b) (4) . No letter was sent.						
09-0172	Imiquimod Cream	Request BE guidance recommendations	Open	3/13/09	5/18/09	(b) (4)
Summary of 09-0172 (b) (4)., Ph.D., Vice President- (b) (4) requested that the OGD provide recommendations regarding the conduct of BE studies on Aldara® (imiquimod) Cream, 5%, sufficient to support the approval of ANDAs and information regarding the appropriate in vitro and/or in vivo studies to conduct to permit approval of a generic product for all of Aldara Cream's approved uses. If one or more comparative clinical studies are recommended, it						

CTL No.	Title	Description	Status	Doc Date	Due Date; Date Closed	From
was requested that OGD provide information regarding the appropriate condition(s) in which to conduct the studies, as well as advice on study design, endpoints, etc.						
09-0214	Imiquimod Cream exclusivity	Request tentative approval for this product	Open	4/6/09		Nycomed
Amy M. Byrom (for Robert J. Anderson, Esq., Vice President, Scientific Affairs) from Nycomed requested that the OGD confirm that it was reviewing the requirements for approval of Imiquimod Cream after ANDA 78-548 was filed and as a result Nycomed will remain eligible and will not forfeit eligibility for 180-day marketing exclusivity if tentative approval is not granted by April1 8, 2009 (30 months after the application was filed). Nycomed further requested that the FDA immediately issue tentative approval for ANDA 768-548.						

Source: compiled by this reviewer based upon a search of the OGD Correspondence Document Tracking System conducted on 6/29/09

Table 8: Imiquimod Cream 5% Protocols Listed in Protocol Database of OGD DBE Tracking System (n=4: 3 Closed, 1 Open)

Protocol Number; Available Documents	Drug Name/ Dosage Form	Firm	Assigned Reviewer	Submission Letter Date; FDA Letter Date	Rec'd Date
P04-022; Draft Clinical Endpoint Protocol (b) (4) to treat external anogenital warts (37 pg)	Imiquimod Cream	(b) (4)	Scardina	4/16/04; 3/11/05 (a)	4/21/04
P04-034; Draft Clinical Endpoint Protocol ALT 0408-01-01 to treat external or perianal warts (60 pg)	Imiquimod Cream 5%	Altana (now Nycomed)	Scardina	6/23/04; 3/11/05 (a)	7/1/04
P04-040; Clinical Endpoint Protocol MIQ 0403 to treat actinic keratosis (27 pg)	Imiquimod Cream 5%	Taro Pharm.	Scardina	8/6/04; 3/18/05 (b)	8/10/04
P07-018; Clinical Endpoint Protocol (b) (4) to treat actinic keratosis (33 pg) and supporting reprints; current submission	Imiquimod Cream 5%	(b) (4)	Hixon	1/27/07	1/30/07

Source: compiled by this reviewer based upon a search of the Protocol Database in the OGD DBE Tracking System conducted on 6/29/09

(a) On March 11, 2005, (b) (4) (submitted P04-022) and Altana, Inc (submitted P04-034) were issued identical, 5-page regulatory letters containing 18 comments regarding a clinical endpoint protocol of Imiquimod Cream, 5%, which included the following comments:

1. The OGD recommends that you conduct a single bioequivalence study with clinical endpoints in the treatment of actinic keratosis (AK) for demonstrating bioequivalence of a generic Imiquimod product to the Reference Listed Drug (RLD), Aldara™ Cream 5%. The OGD believes that AK is the most discriminatory treatment indication for this product.
2. In a bioequivalence study with clinical endpoints, the duration of study treatments and total number of treatment doses received should be the same for all patients treated. The endpoint for evaluation should also be the same within a pre-specified visit window to minimize any variability in the evaluation of treatment response. For treatment of external anogenital warts, the recommended treatment duration is variable, with the treatment being stopped at the time of complete clearance.
3. The treatment regimen for this AK study should be twice weekly applications for 16 weeks for all patients. The cream should be applied to the entire treatment area at each application. Patients should not apply more than one packet to the contiguous treatment area at each application. It is recommended that you closely follow the dosing instructions in the approved label for this product.
4. Patients should have at least 4 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on face or scalp for entry.
5. The primary endpoint, proportion of patients with complete clearance of AK lesions, should be evaluated at week 24 (8 weeks after the end of treatment). The acceptable visit window should be within $\pm$ 7 days for the patient to be included in the evaluable per protocol (PP) population for analysis.

6. To establish bioequivalence, the 90% confidence interval of the proportional difference in cure rates between test and reference products must be within (-0.20 and +0.20), using the PP study population.
7. To assure that the study design is sensitive enough to show a difference between products, the test and reference products should both be statistically superior to placebo ($p<0.05$) with regard to the cure rate at week 24, using the intent-to-treat (ITT) study population and Last Observation Carried Forward (LOCF).
8. The accepted PP population used for bioequivalence evaluation includes all randomized patients who apply a pre-specified proportion of doses of the assigned medication and complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation. Patients discontinued for lack of treatment effect should also be included in the per protocol population as treatment failures. The protocol should specify how treatment compliance would be verified, e.g., by the use of patient diaries.
9. Please be advised that the information given in this letter is general in nature. The OGD recommends that you submit protocols to the Clinical Review Team for review and comment prior to conducting bioequivalence studies with clinical endpoints.

(b) On March 11, 2005, Taro Pharmaceuticals U.S.A., Inc. (submitted P04-040) was issued a 6-page regulatory letters containing 21 comments regarding a clinical endpoint protocol of Imiquimod Cream, 5%, which included the following 5 comments specific for Imiquimod Cream and dermatology protocols:

1. In order to appropriately evaluate a study for bioequivalence, each patient must receive the same dosing regimen and the same duration of therapy. Therefore, patients that show complete clearing prior to 16 weeks should continue treatment up to 16 weeks, unless the patient can no longer tolerate the use of study medication.
2. Patients should not apply more than one packet to the contiguous treatment area at each application. It is recommended that the dosing instructions in the approved label for this product are closely followed.
3. You should identify in your protocol what type of sunscreen and moisturizer will be provided to the patients. All patients should be instructed to use the same sunscreen and moisturizer.
4. Patients should be instructed not to use any type of bandage or occlusive on the treatment area.
5. You should consider irritation as an adverse event at any time during the study. Patients that are discontinued due to severe irritation should be excluded from the PP population and included in the ITT population using LOCF, unless the patients complete 75% of the total prescribed doses of study drug. The incidence of irritation should be compared between treatment groups.

Table 9: Imiquimod Cream 5% ANDA Submissions (n=4)

ANDA No. Sponsor	Submission Type	Letter Date	Stamp Date	Action
(b) (4)	(b) (4)			(b) (4)
	WD-sponsor requested to withdraw NDA from review and stop 180 day clock			WU-ANDA Withdrawn from Pending
78-548 Nycomed US Inc. [**NOTE**: Corporate name was changed from Altana Inc to Nycomed US Inc on 9/24/07]	Original	10/16/06	10/17/06	Pending (c)
	MC (new correspondence)	10/19/06	10/20/06	
	MC (reviewer aid amendment-additional toxicology summaries)	12/4/06	12/6/06	
	MC	12/20/06	12/21/06	
	MC (telephone amendment; justification for (b) (4) oleic acid inactive ingredient)	1/9/07	1/10/07	
	MC (telephone amendment)	1/11/07	1/12/07	
	XP	1/17/07	1/18/07	
	XP	3/19/07	3/20/07	
	AM (minor amendment-response to chemistry deficiencies letter dated 3/20/07)	3/30/07	4/3/07	
	AB	4/27/07	4/30/07	
	AM (telephone amendment-requested information)	5/11/07	5/14/07	

ANDA No. Sponsor	Submission Type	Letter Date	Stamp Date	Action
	MC (telephone amendment)	5/30/07	5/31/07	
	EDR Sequence 0000: AM (minor amendment; response to 7/30/07 FDA correspondence citing Chemistry deficiencies)	10/2/07	10/2/07	
	EDR Sequence 0001: AF and XA (corporate name change from ALTANA inc to Nycomed US Inc and labeling amendment in response to 1/10/08 FDA correspondence citing labeling deficiencies)	1/22/08	1/23/08	
	EDR Sequence 0002: AF (labeling amendment in response to 2/12/08 FDA telephone request for patient information reformatted into a stand-alone document)	2/13/08	2/14/08	
	EDR Sequence 0003: AB (BE amendment containing response to 3/19/08 clinical team request for CRFs, IRB approval letter and manufacturing date of test product)	3/28/08	3/31/08	
	EDR Sequence 0004: AA (Gratuitous amendment to request approval for foilpac and provide update on investigation of high assay results)	6/12/08	6/12/08	
	EDR Sequence 0005: AM (response to FDA 7/24/08 CMC telephone request for additional information on residual solvents)	7/24/08	7/25/08	
	EDR Sequence 0006: AM (response to FDA 7/30/08 CMC telephone request for additional information on residual solvents)	8/15/08	8/15/08	
	EDR Sequence 0007: AM (response to FDA 8/18/08 CMC telephone request)	8/22/08	8/22/08	
	EDR Sequence 0008: AM (response to FDA 8/27/08 CMC telephone request)	8/28/08	8/28/08	
	EDR Sequence 0009: AM (response to FDA 3/13/09 CMC telephone request)	3/13/09	3/16/09	
	EDR Sequence 0010: MC (sponsor requested meeting to discuss potential changes to the requirements for approval of Imiquimod Cream and to agree on steps that Nycomed may take to help OGD issue a Tentative Approval)	3/17/09	3/17/09	
	EDR Sequence 0011: MC (sponsor requested that the OGD confirm that it was reviewing the requirements for approval of Imiquimod Cream after ANDA 78-548 was filed and as a result Nycomed will remain eligible and will not forfeit eligibility for 180-day marketing exclusivity if tentative approval is not granted by April1 8, 2009 (30 months after the application was filed). Sponsor further requested that the FDA immediately issue tentative approval for ANDA 768-548.)	4/1/09	4/2/09	
78-837 Perrigo Israel	EDR Sequence 0000: Original (containing the results of clinical endpoint study PRG-901: 24-week (16 week treatment period and 8 week follow-up period), 2:2:1 randomized, double-blind, vehicle-controlled, parallel, multiple site, efficacy and safety study in 440 subjects of test product vs. RLD vs. cream vehicle of test product, applied topically twice a week for 16 weeks for the treatment of 4-15 actinic keratosis lesions of the face or anterior bald scalp within a contiguous 25-cm^2 treatment area; primary efficacy variable was rate of complete clearance, defined as the % of subjects in whom no AK lesions were visible in the target area at the follow-up visit at 8 weeks post-treatment)	3/15/07	3/20/07	Pending (d)

ANDA No. Sponsor	Submission Type	Letter Date	Stamp Date	Action
	EDR Sequence 0001: XP (documentation of sending and receipt of patent certification notice to innovator)	7/4/07	7/9/07	
	EDR Sequence 0002: XP (documentation of Perrigo not receiving any notice during the waiting period that named parties would take legal action against Perrigo for patent infringement resulting from Perrigo's ANDA filing)	9/17/07	9/21/07	
	EDR Sequence 0003: AM (minor amendment in response to 9/25/07 chemistry deficiency letter)	12/2/07	12/5/07	
	EDR Sequence 0004: AF (response to labeling deficiency 1/10/08 letter and submission of SPL)	3/14/08	3/21/08	
	EDR Sequence 0005: AF (provides a clearer version of the .pdf file of the final printed labeling in response to OGD Labeling Review Division 4/3/08 telephone request)	4/15/08	4/21/08	
	EDR Sequence 0006: AF (provides final printed labeling for the Patient Information in response to OGD Labeling Review Division 4/22/08 e-mail request)	5/1/08	5/6/08	
	EDR Sequence 0007: AM (minor amendment in response to 7/28/08 chemistry deficiency letter(	11/27/08	12/1/08	
91-044 Tolmar (Sandoz is a marketing partner for Tolmar)	Original (one volume containing required signed original documentation to accompany the electronic CTD version copy)	12/16/08	12/18/08	Pending (e)
	EDR Sequence 0000: MC [new correspondence consisting of one DVD-ROM containing electronic CTD version of Original ANDA submission containing the results of clinical endpoint study SYM 2007-08: 24-week (16 week treatment period and 8 week follow-up period), 3:3:1 randomized, double-blind, vehicle-controlled, parallel, multiple site, efficacy and safety study in 474 subjects with at least 4 actinic keratosis lesions within a 25 cm^2 contiguous area on the face or scalp but not both concurrently and evaluating test product vs. RLD vs. cream vehicle of test product, applied topically twice weekly for 16 weeks; primary efficacy variable was rate of complete clearance, defined as the % of subjects in whom no AK lesions were visible in the target area at the follow-up visit at 8-weeks post-treatment.]	12/24/08	12/30/08	
	EDR Sequence 0001: MC (new correspondence telephone amendment providing revised paragraph III certification, corrected environmental impact analysis statement and revised stability protocol, including accelerated stability conditions)	3/27/09	3/30/09	
	EDR Sequence 0002: MC (new correspondence telephone amendment provided revised paragraph III certification including expiration dates for all original patents and pediatric extensions)	4/3/09	4/6/09	
	EDR Sequence 0003: AC (telephone amendment providing SYM 2007-08 Investigator's Table with investigator addresses and number of patients per site)	5/13/09	5/14/09	

Source: compiled by this reviewer based upon a search of the OGD Master Que, DSS, DFS and EDR conducted on 6/29/09

DFS=Division File System; DSS=Decision Support System; EDR=Electronic Document Room; RLD=Reference Listed Drug

(a) Regarding ANDA (b) (4) submitted by (b) (4) letter was issued on (b) (4) due to the following reasons:

The preliminary ANDA filing review showed that your product fails to meet the bioequivalence acceptance criteria. You are strongly urged to contact the Clinical Review Team for further assistance prior to conducting a new BE study for this product. You may contact Debbie Catterson, R.Ph at (301) 827-7301.

[redacted] (b) (4)

[redacted] (b) (4)

(b) Regarding ANDA [redacted] (b) (4) submitted by [redacted] (b) (4)

Your study did not meet the acceptable bioequivalence [redacted] (b) (4)

To be acceptable for filing, your data must demonstrate that your product is bioequivalent to the RLD using the [redacted] (b) (4). Your product is not shown to be bioequivalent to the RLD because it failed to [redacted] (b) (4) for approval of the product. Therefore, your application is not acceptable for filing from the Clinical Review Team perspective.

(c) ANDA 78-548 by Nycomed (formerly known as Altana) has twice been issued "not approvable" chemistry letters on 3/20/07 (due to minor deficiencies based upon a 38-page Chemistry Review finalized in DFS on 3/20/07) and on 7/30/07 (due to minor deficiencies based upon a 117-page Chemistry Review finalized in DFS on 7/30/07). On 12/19/07, it was determined that chemistry was ok, pending EES, labeling and Bio. Labeling was determined to be deficient on 1/10/08. Labeling Approval Summary #1 was finalized in DFS on 2/19/08. Inactive ingredient consult (oleic acid) consult conveyed to OND on 4/8/08; however, review team not copies in DFS and Consult 2007-0102 resent on 1/26/09 and assigned to R. Dorsam on 1/29/09. On 4/1/09, the Office of Compliance (OC) issued an acceptable recommendation. On 4/16/09, OGD sent sponsor a letter confirming that FDA is currently reviewing the approval requirements for ANDAs for Imiquimod Cream, 5% and under section 505(j)(5)(D0(IV) of the Federal Food, Drug and Cosmetic Act, the review of the requirements for approval of an application may be a factor in whether an applicant will forfeit eligibility for 180-day exclusivity described in section 505(j)(5)(B)(iv).

(d) ANDA 78-837 by Perrigo Israel Pharmaceuticals Ltd. has twice been issued "not approvable" chemistry letters on 9/25/07 (due to minor deficiencies, including an inadequate DMF, based upon a 51-page Chemistry Review finalized in DFS on 9/25/07 for the Original ANDA) and on 7/28/08 (due to minor deficiencies based upon a 32-page Chemistry Review finalized in DFS on 7/26/08 for the 12/2/07 Amendment). DSI has completed an inspection of three clinical sites for protocol PRG-601 and one site was issued a form FDA-483 (due to one subject applying study medication to an incorrect site for 5 weeks and the start and end dates of one adverse event for one subject not being documented in the subject diary or not agreeing with the case report form). The Office of Compliance (OC) issued an "acceptable" recommendation on 7/15/07. Labeling Approval Summary #1 was finalized in DFS on 5/12/08. Due to first filer not securing approval within 30 months, firm wishes to request expedited review.

(e) ANDA 91-044 by Tolmar is an electronic submission (see EDR for Sequences 000, 0001, 0002 and 0003).

Following this page, 9 pages withheld in full - (b)(5) Draft Guidance

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

/s/

Brenda Gierhart
7/17/2009 10:29:43 AM
MEDICAL OFFICER

Dena Hixon
7/17/2009 10:34:39 AM
MEDICAL OFFICER
I concur.

Gary Buehler
7/17/2009 04:38:48 PM
DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-548

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pharma

ALTANA

78-548

October 16, 2006

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

Original Submission
Abbreviated New Drug Application
Imiquimod Cream 5%

Dear Sir or Madam:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94, ALTANA Inc is submitting this Abbreviated New Drug Application to market a new drug, **Imiquimod Cream 5%.**

The Reference Listed Drug (RLD) that is the basis for this submission is Aldara™ (imiquimod) Cream, 5% by 3M Pharmaceuticals, NDA 20-723.

The proposed drug, Imiquimod Cream 5% contains the same active ingredient and is identical in strength, dosage form and route of administration to the RLD. All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide Database (October 5, 2006). Currently, the Inactive Ingredient Guide Database does not contain a maximum potency listing for oleic acid in a topical cream formulation. A rationale and supportive information for the use of the oleic acid amount in the proposed formulation have been included in this submission (Section 3.2.P.1) as advised by the Office of Generic Drugs, Regulatory Support Branch in August 2005. ALTANA has prepared multiple exhibit batches of the proposed drug product and has included a comprehensive Chemistry, Manufacturing and Controls (CMC) package with this submission. Both exhibit batches have demonstrated successful stability data at multiple storage conditions in accordance with ICH guidelines. ALTANA has conducted a successful full clinical endpoint bioequivalence study with the RLD and the proposed drug. The two products were found to be bioequivalent and exhibited similar safety profiles during the conduct of the study. Oleic acid has been used in Food, Drug and Cosmetics and is therefore safe for this application.

Electronic copies of the Quality Overall Summary and the Clinical Summary are also provided in the front cover of volume 1 of the application. All files are provided in Word format.

All regulatory correspondence related to this Abbreviated New Drug Application should be addressed to:

Ms. Audrey Zaweski
Director, Regulatory Affairs
ALTANA Inc
PO Box 2006
60 Baylis Road
Melville, NY 11747
Telephone: (631) 454-7677 X 3007
Facsimile: (631) 756-5114

A certified copy of the complete submission is being sent to the New York District Office under separate cover.

Please advise if you require any additional information.

Sincerely,

ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RJA/ab

Enclosures

Pharma

ALTANA

October 19, 2006

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Mr. Harvey Greenberg
Special Assistant (HFD-612)
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855

VIA FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%

Dear Harvey:

As per our conversation, I've enclosed an original and a copy of the missing page two (2) of the original cover letter. Please add this to the files.

Thank you so much for your help.

If you have any questions, please call me at (631) 454-7677 ext. 2091.

Sincerely,

ALTANA Inc

Virginia

Virginia Carman
Associate Director, Regulatory Affairs

VC:ab

Two patents are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for the RLD:

1. Patent Number 4,689,338, expires August 25, 2009
2. Patent Number 5,238,944, expires August 24, 2010

ALTANA certifies to both patents in Section 1.3.5 with a Paragraph III Certification for Patent '338 and a Paragraph IV Certification for Patent '944. Regarding the Paragraph IV Certification, ALTANA will comply with:

1. the requirements under § 314.95(a) with respect to providing notice to each of the following persons: the owner of the patent or their representative and the holder of the approved application for the listed drug
2. the requirements under § 314.95(c) with respect to content of the notice.

This submission contains two exhibit batches, #T045 and W346. Batch #T045 was fully packaged utilizing the 0.25 gram foilpac presentation for which approval is currently requested. Additional alternative package sizes were also utilized, but are not being pursued for approval. Batch #W346 was only packaged in the 0.25 gram foilpac. The number of units filled for each packaging size and the disposition of any remaining bulk product are reconciled in each exhibit batch record.

Included in this submission, along with the Form FDA 356h, are the required Patent Status and Exclusivity Statements; Draft Labeling; full Components and Composition statements; Raw Materials Controls, description of the Manufacturing Facilities, Manufacturing and Processing Instructions, In-Process Controls, Filling and Packaging procedures; Container/Closure System; controls for the Finished Dosage Form, Analytical Methods; Stability of the Finished Dosage Form; Environmental Assessment, Certification Requirements of the Generic Drug Enforcement Act of 1992 and a Bioequivalence Study.

An electronic copy of the proposed labeling is provided in the front cover of volume 1 of the application. All files are provided in PDF format (version 6.0). The package insert has also been provided in SPL format. Module 1.14.1 of the paper ANDA also includes draft labeling for the proposed product along with the RLD labeling. In addition, Module 1.14.3.1 contains annotated side-by-side comparisons as well as the labeling limitation statement.

An electronic copy of the bioequivalence data is provided in the front cover of the first volume containing the Bioequivalence Study. All study data is prepared on CD-ROM in SAS transport files (Version 5). The CD-ROM also includes the appropriate data definition file (description of each SAS file and its contents and definition of each dataset variable) prepared in Adobe Acrobat.

ORIGINAL

Pharma

ALTANA

N/MC

December 4, 2006

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Martin Shimer
Branch Chief, Regulatory Support Branch
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-615) Room 104
7500 Standish Place
Rockville, MD 20855

VIA TELEFAX (301) 827-5911 and FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
Amendment-Reviewer Aid

Dear Mr. Shimer:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%. The Reference Listed Drug (RLD) that is the basis for this submission is Aldara™ (imiquimod) Cream, 5% by 3M Pharmaceuticals, NDA 20-723. This submission contained a Paragraph IV certification with respect to US patent number 5,238,944. The information contained in the original ANDA should be considered a complete submission and as such "Acceptable for Filing". The purpose of this amendment is to provide a reviewer aid.

ALTANA's original ANDA submission contained a full bioequivalence study which successfully demonstrated that the test and reference products were equivalent. As stated in the original submission, the proposed drug Imiquimod Cream 5% contains the same active ingredient and is identical in strength, dosage form and route of administration to the RLD. All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide Database (October 5, 2006). The proposed drug contains oleic acid which is not currently listed in the Inactive Ingredient Guide Database for a topical cream formulation. In addition to the bioequivalence study which demonstrated that the use of oleic acid did not produce a different safety and efficacy profile, a toxicology safety summary was also included.

With this amendment, ALTANA is providing *in-vitro* data from two studies (MROR and Cadaver Skin), which further demonstrate no significant differences between the test and reference formulations. ALTANA is also providing two additional toxicology summaries. This information should be considered a "Reviewer Aid" to be used by each of the specific disciplines when reviewing the submission.

If you have any questions or require additional information please contact Audrey Zaweski at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RA:tl

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# _____78-548_____**FIRM NAME**__Altana Inc.

DRUG NAME _Imiquimod Cream, 5%_____

DOSAGE FORM ___Topical Cream_____

Requested by: _____Eda Howard_____ Date: _11/13/06_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Reason:
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **_X_COMPLETE** **___INCOMPLETE**

Reviewed by:

_____ Date: _____
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				IRB #05-4576-0 was approved on December 2, 2005. However, a copy of IRB approval letter was not submitted.
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				Any deviations were noted under "Comments/16.2.13".
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				Available in EDR
Study Results	X				

Clinical Raw Data/ Medical Records	X				
Composition	X				Available in EDR
BioStudy Lot Numbers	X				
Date of Manufacture		X			Manufacture date of the test product was not provided in the study report.
Exp. Date of RLD		X			Expiration date of the RLD was not provided in the study report.
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				
Waiver requests for other strengths / supporting data		X			N/A

Additional Comments regarding the ANDA:

1. According to the sponsor's analysis, the 90% CI of the difference in success (100% clearance of AK, score of 0) rates between the test and reference products in the PP population at week 24 (8 weeks follow-up) is -0.08 and 0.09, which is within acceptable limits of -0.20 and +0.20. Both active drug products show superiority over the vehicle group in the mITT population ($P<0.05$).Therefore, the sponsor's data support that their product is BE to the RLD.
2. Based on the OGD's response (2/24/05) to their control document (OGD#04-034, Altana), Altana conducted a BE study in patients with AK.
3. The sponsor's formulation includes (b) (4) (%w/w) of oleic acid. This concentration of inactive ingredient exceeds the maximum concentration previously approved by the Agency in a topical drug product.

4. In volume 2.1, the sponsor provided animal studies and additional data in support for justification of safety of the concentration of inactive ingredient (oleic acid) proposed in their formulation. This information will be sent for Pharm-Tox consult by Regulatory Support Branch.
5. The OGD received a citizen petition (docket no. 2004P-0057; submission dated 12/21/04) by Valeant Pharmaceutical International regarding Efudex that questions acceptability of BE study only in actinic keratosis (AK) when this product is indicated for treatment of both AK and superficial basal cell carcinomas (sBCC). Therefore, the OGD recommendation for establishing BE of Aldara Cream 5% may change based on the outcome of this petition response.
6. The following information was not submitted in the study report:

- manufacture date of the test product
- expiration date of the reference product
- a copy of IRB approval letter

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

/s/

Carol Y. Kim
12/6/2006 11:50:20 AM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
12/6/2006 12:14:26 PM
MEDICAL OFFICER

Pharma

ALTANA

December 20, 2006

MC.

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Branch Chief, Regulatory Support Branch
Office of Generic Drugs
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Food and Drug Administration
Metro Park North II (HFD-615) Room 104
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VIA TELEFAX (301) 827-5911
and FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
REQUEST FOR IMMEDIATE DETERMINATION OF ACCEPTANCE TO FILE ANDA WITH PARAGRAPH IV CERTIFICATION, TO START 30-MONTH STAY CLOCK

Dear Mr. Shimer:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream 5%. The Reference Listed Drug (RLD) that is the basis for this submission is Aldara™ (imiquimod) Cream, 5% by 3M Pharmaceuticals, NDA 20-723. This submission contained a Paragraph IV certification with respect to US patent number 5,238,944. ALTANA requests FDA's immediate determination of acceptance to file ANDA 78-548 in order to complete its Paragraph IV certification notice obligations which, in turn, trigger the 45-day window for a patent infringement suit and, potentially, the 30-month Stay clock under FDA's 180-day Exclusivity rules (21 CFR 314.107).

Reference is also made to the telephone inquiries regarding the status of the above referenced submission made by ALTANA representatives to the Regulatory Support Branch on December 1 and December 18, 2006. ALTANA acknowledges that the Regulatory Support Branch is "back-logged" with applications and currently under-staffed. However, the Aldara™ product on which ALTANA's submission is based represents a significant market opportunity and a significant investment for ALTANA. It is imperative that this application be given immediate attention such that an acceptance decision, in accordance with 21 CFR 314.101(a)(1), can be made without further delay. FDA's regulation requires a 60-day review for acceptance to file decisions, and the 60-day period for ALTANA's ANDA expired on or about December 16, 2006. As you know, ALTANA's ability to provide prompt, proper notification to the patent and NDA holders is vital to the Paragraph IV certification process. ALTANA cannot begin this process without the prerequisite ANDA acceptance acknowledgement from FDA, pursuant to 21 CFR 314.95(b).

If you have any questions or require additional information, please contact Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA Inc

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RA:tl

Pharma

ALTANA

January 9, 2007

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MC

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (HFD-600) Room 286
7519 Standish Place
Rockville, MD 20855

VIA FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT

Dear Mr Buehler:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on January 8, 2007 between Iain Margand and ALTANA representatives in which FDA requested additional information.

This correspondence has been identified as a **TELEPHONE AMENDMENT**. Each item has been addressed in **comment** / response format.

1. **Provide a cGMP statement for** (b) (4)
   A cGMP statement for (b) (4) is included as **Attachment I.**

2. **Provide a dimensional drawing for the foilpac presentation.**
   A dimensional drawing for the foilpac presentation is included as **Attachment II.**

3. **Provide electronic copies of pharmacology and toxicology information submitted on October 16, 2006 & December 4, 2006.**
   Electronic copies of pharmacology and toxicology information submitted on October 16, 2006 & December 4, 2006 have been provided on a CD-Rom included with this submission. **Attachment III** contains a tabular listing of the pharmacology and toxicology information included on the CD-Rom.

If you have any questions or require additional information please contact Audrey Zaweski at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RA:tl

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-548

Altana Inc.
Attention: Robert J. Anderson
P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated January 8, 2007 and your correspondence dated January 9, 2007.

NAME OF DRUG: Imiquimod Cream, 5%

DATE OF APPLICATION: October 16, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 17, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Rosalyn Adigun
Project Manager
301-827-5848

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
1/10/2007 02:51:44 PM
Signing for Wm Peter Rickman

Pharma

ALTANA

ORIGINAL

January 11, 2007

ALTANA Inc
60 Baylis Road
P.O. Box 2006
Melville, NY 11747-0103
USA
T +1 (631) 454-7677
www.altanainc.com

Martin Shimer
Branch Chief, Regulatory Support Branch
Office of Generic Drugs, Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-615) Room 104
7500 Standish Place
Rockville, MD 20855

VIA TELEFAX (301) 827-5911 and FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT

ORIG AMENDMENT
N-000-MC

Dear Mr Shimer:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on January 10, 2007 between FDA and ALTANA representatives in which FDA requested additional information.

This correspondence has been identified as a **TELEPHONE AMENDMENT**. Each item has been addressed in **comment** / response format.

1. **Provide an explanation of which group listed in the ANDA is responsible for testing drug substance.**
   All drug substance testing is currently performed at ALTANA, Melville NY. (b) (4) (b) (4) and (b) (4) have been designated as alternate sites for all drug substance testing.

2. **Provide an explanation of which group listed in the ANDA is responsible for testing drug product.**
   All drug product testing is currently performed at ALTANA, Melville NY. (b) (4) and (b) (4) have been designated as alternate sites for all drug product testing.

If you have any questions or require additional information please contact Audrey Zaweski at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

Audrey Zaweski for
Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RECEIVED
JAN 12 2007
OGD / CDER

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 78-548 **FIRM NAME**: ALTANA INC.

PIV: YES **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: IMIQUIMOD
DOSAGE FORM: CREAM, 5%

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☒ **BCE**	
☐ **BST**	☐ **BDI**	

Random Queue: 3
Chem Team Leader: Fan, Jim PM: Rosalyn Adigun Labeling Reviewer: Beverly Wietzman

Letter Date: OCTOBER 16, 2006 **Received Date**: OCTOBER 17, 2006

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 4020900 OTHER DERMATOLOGIC AGENTS

Archival copy: PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand Date 1/10/07	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

1/8/07 Requested cGMP for [redacted], outside lab, that cites 21 CFR 210 and 211, not just accreditation information.
Requested dimensional drawings for container.
Requested Pharm/Tox data for Oleic Acid submitted electronically for consult.

Lot T045 packaged in [redacted] foil [redacted] which is no longer available. A second batch utilizing [redacted] foil [redacted], lot W346, was produced. Seeking approval of 0.25 g container size only, though exhibit batch packaged in [redacted] and [redacted] container sizes (lot T045 only).

Amount of Oleic Acid used in drug product is more than in previously approved product. Applicant has provided Pharm/Tox information with the application which will be sent on consult.

Contact: Audrey Zaweski 631-454-7677 X3007

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: OCTOBER 16, 2006 See vol. 2.1 for page two	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations Yes **1.3.5.2** **Patent Certification** 1. Patent number(s) PIII '338 exp. 8/25/09 PIV '944 exp. 8/24/10 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ No Relevant Patents ☐ 3. Expiration of Patent(s): 8/24/2010 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES I-433 exp. 7/14/07 I-420 exp. 3/2/07	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 20-723 Ref Listed Drug: ALDARA Firm: 3M PHARMACEUTICALS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Imiquimod 3. Inactive ingredients Same except for use of Oleic Acid 4. Route of administration Topical 5. Dosage Form Cream 6. Strength 5%	☒
1.12.14	**Environmental Impact Analysis Statement**	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): PAPER, NA	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _____PDF (archive) X__ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _____ YES X___ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix N/A**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** **3.2.S.1.2** **Structure** **3.2.S.1.3** **General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API DMF # (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG Oleic Acid amount will need to be sent on consult	☐
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** Y **3.2.P.3.5** **Process Validation and/or Evaluation** N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** Y **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form Y Lots T045 and W346 **3.2.P.5.5** **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period 24 months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y T045 2. Batch numbers on stability records the same as the test batch W346	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S** **Comparability Protocols N/A** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation See Attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** Y **3.2.R.2.P** **Comparability Protocols** N/A **3.2.R.3.P** **Methods Validation Package** Y Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 5

CLINICAL STUDY REPORTS See Bio First Generic Review

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES/STU/ BIO CLINICAL TEAM 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

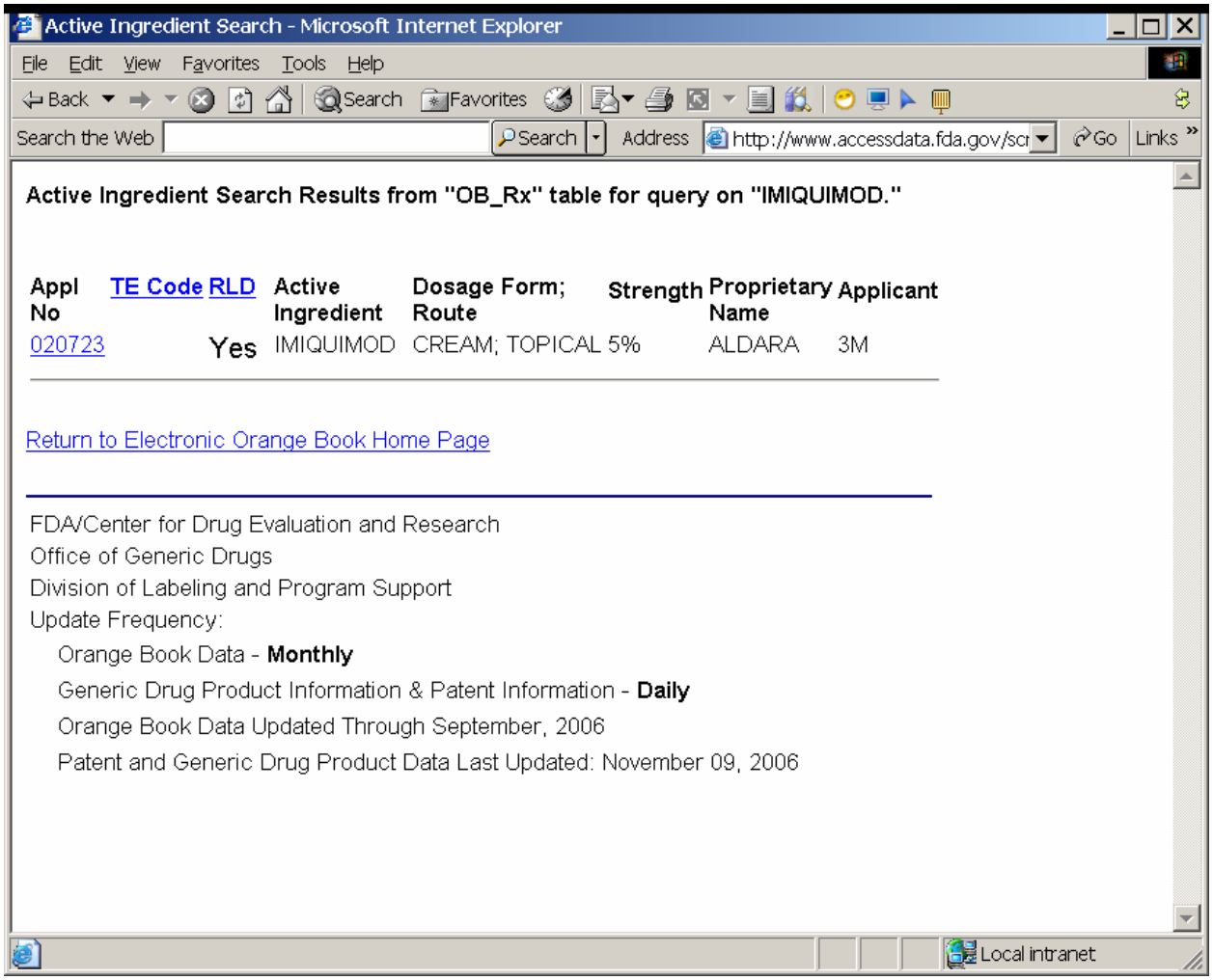
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina

Table 2.3.P.1-1 The Composition of Imiquimod Cream 5%

Ingredient	Quality	Function	Amount % w/w	Batch Quantity per (b) (4) (b) (4)

Following this page, 4 pages withheld in full - (b)(4)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Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scr Go Links
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Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
020723
Yes
IMIQUIMOD
CREAM; TOPICAL
5%
ALDARA
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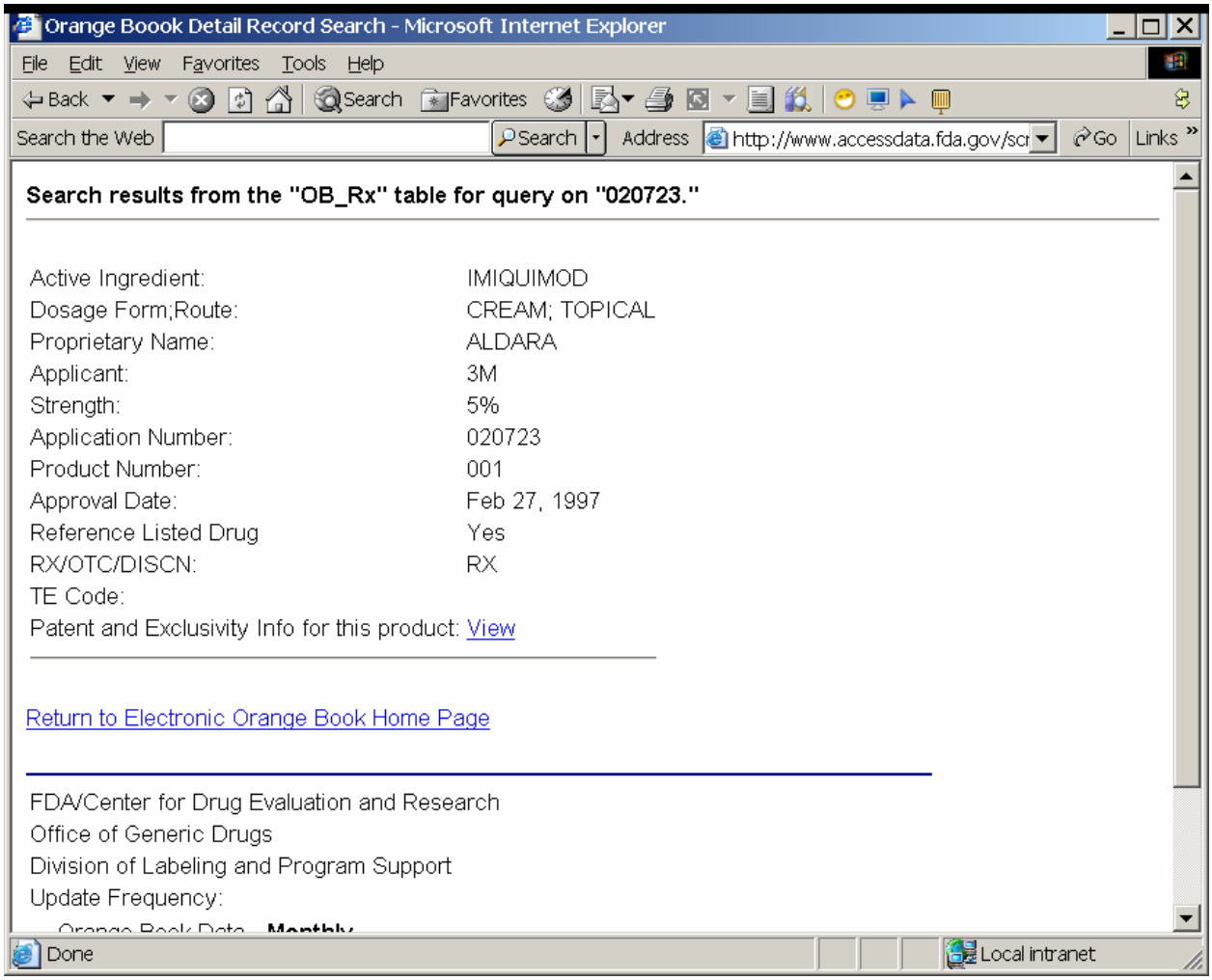
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through September, 2006
Patent and Generic Drug Product Data Last Updated: November 09, 2006
Local intranet


Orange Boook Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scr Go Links
Search results from the "OB_Rx" table for query on "020723."
Active Ingredient: IMIQUIMOD
Dosage Form;Route: CREAM; TOPICAL
Proprietary Name: ALDARA
Applicant: 3M
Strength: 5%
Application Number: 020723
Product Number: 001
Approval Date: Feb 27, 1997
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
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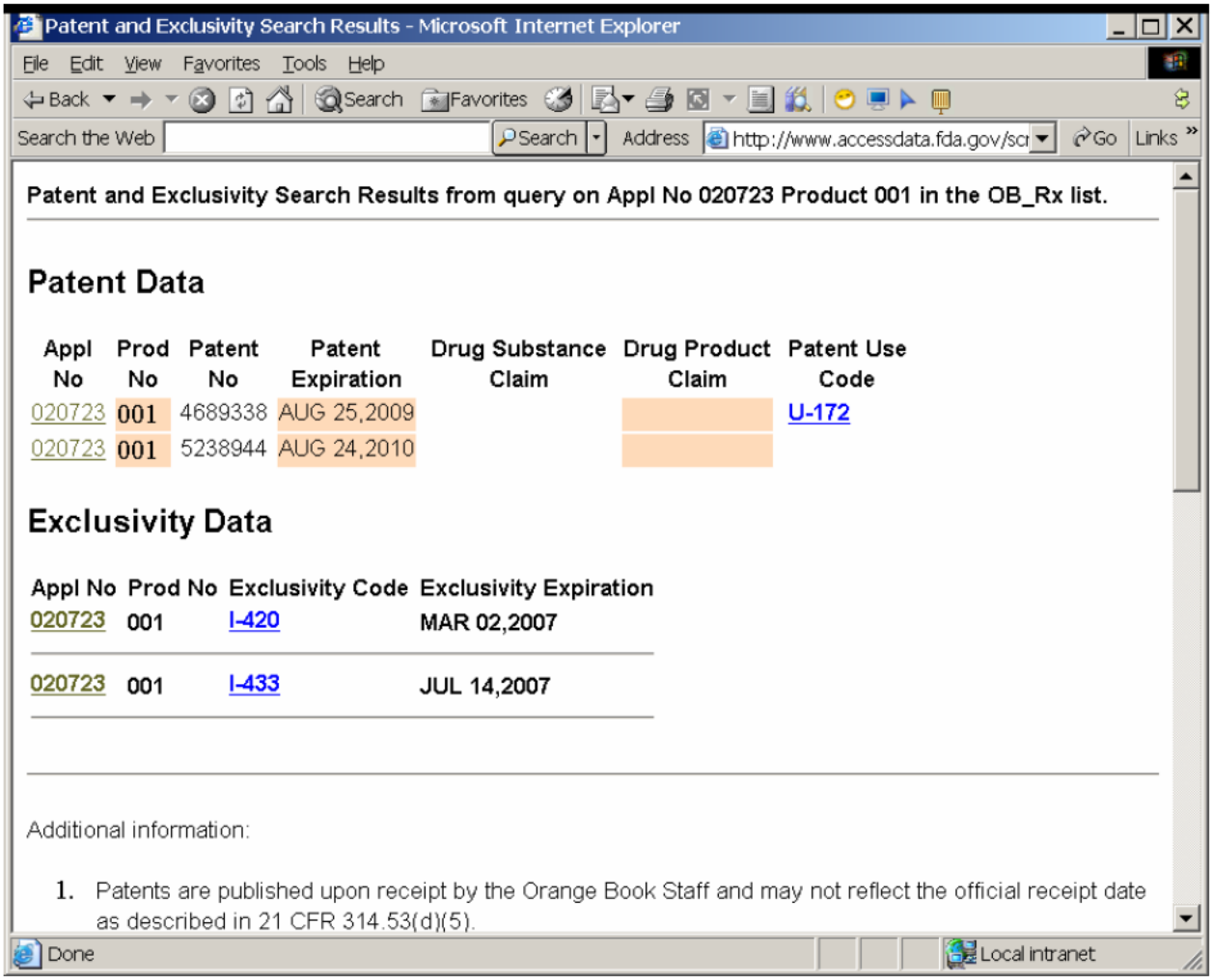
Patent and Exclusivity Search Results - Microsoft Internet Explorer
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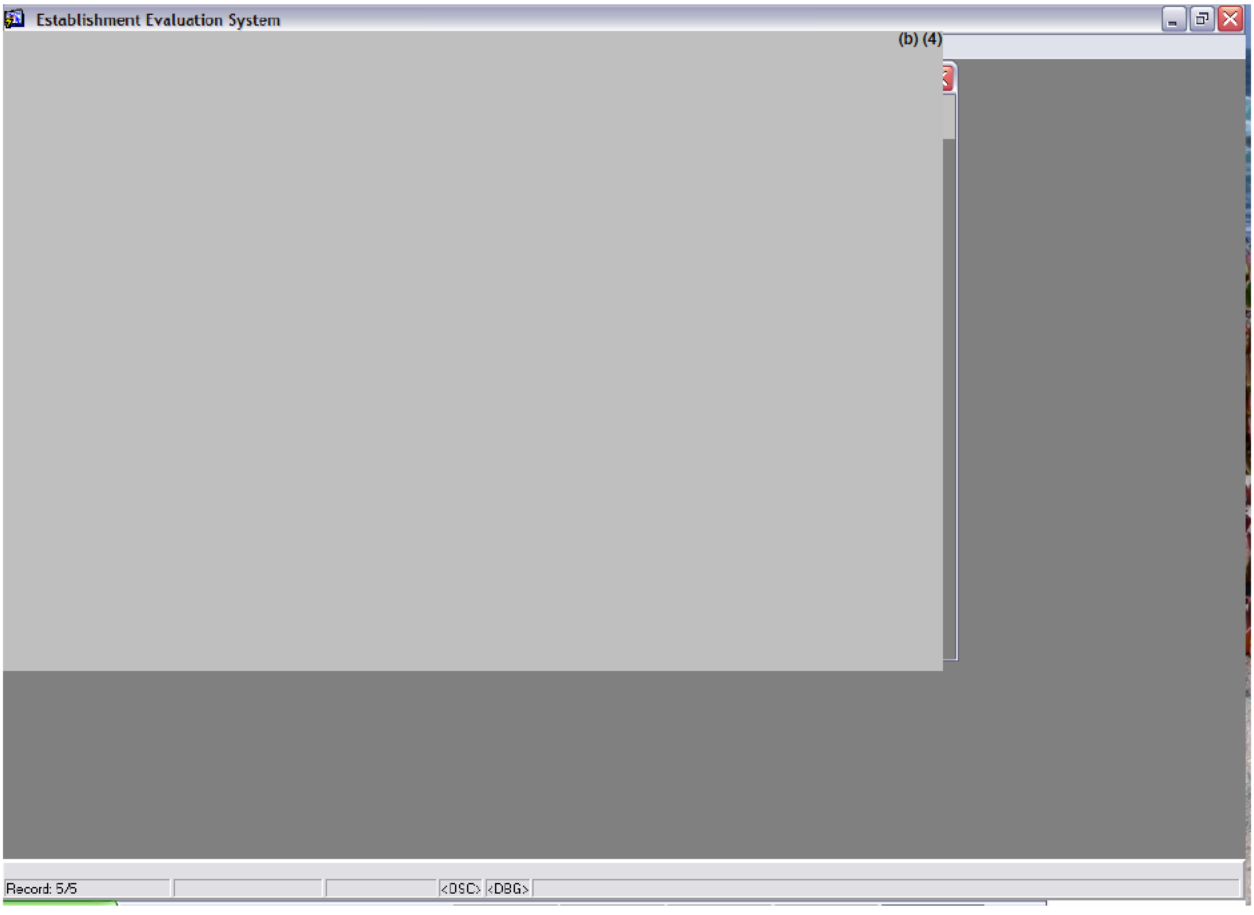
Back Search Favorites
Search the Web Search Address http://www.accessdata.fda.gov/scr Go Links
Patent and Exclusivity Search Results from query on Appl No 020723 Product 001 in the OB_Rx list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code
020723 | 001 | 4689338 | AUG 25,2009 | | | U-172
020723 | 001 | 5238944 | AUG 24,2010 | | |
Exclusivity Data
Appl No | Prod No | Exclusivity Code | Exclusivity Expiration
020723 | 001 | I-420 | MAR 02,2007
020723 | 001 | I-433 | JUL 14,2007
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
Done
Local intranet


Establishment Evaluation System
(b) (4)
Record: 5/5

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

/s/

Martin Shimer

1/16/2007 11:26:50 AM

Pharma

ALTANA

N/xp

January 17, 2007

ALTANA Inc
60 Baylis Road
P.O. Box 2006
Melville, NY 11747-0103
USA
T +1 (631) 454-7677
www.altanainc.com

Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4
7519 Standish Place, Rm. 286
Rockville, Maryland 20855

notice of PIV cert sent with RR date of 1/16/07. 45 day time period would end 3/2/07.

JR. ***VIA FEDERAL EXPRESS***

ANDA 78-548
Imiquimod Cream 5%
PATENT AMENDMENT – DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

Dear Mr. Buehler:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to FDA's January 10, 2007 correspondence confirming that ALTANA's ANDA, which contains a Paragraph IV patent certification, is acceptable for filing. In accordance with the requirements set forth in 21 CFR § 314.95(b), ALTANA hereby certifies that it has provided notice to each person identified under 21 CFR § 314.95(a) and that the notice met the content requirements under 21 CFR § 314.95(c).

In accordance with the requirements set forth in 21 CFR § 314.95(e), ALTANA is amending this abbreviated application to provide documentation of receipt of the notice under paragraph (a) of § 314.95 by each person provided the notice. Please refer to **Attachment I.**

As requested, ALTANA commits to submitting (1) notification that litigation has occurred within the 45-day period or (2) confirmation that no legal action has been taken immediately after the 45-day period has elapsed.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RJA:tl

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2007-0102**	
TO *(Division/Office)* DDOP - HFD-150 Thru: Glen Jones, OODP HFD-106			FROM: Iain Margand	
DATE: 1/26/2007	IND NO.	ANDA NO. 78-548	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 1/8/2007,
NAME OF DRUG Imiquimod Cream		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG topical treatment for basal cell carcinoma	DESIRED COMPLETION DATE 3/27/2007
NAME OF FIRM Altana Inc.				

REASON FOR REQUEST

I. GENERAL

✆ NEW PROTOCOL	✆ PRE NDA MEETING	✆ RESPONSE TO DEFICPENCY LETTER
✆ PROGRESS REPORT	✆ END OF PHASE II MEETING	✆ FINAL PRINTED LABELING
✆ NEW CORRESPONDENCE	✆ RESUBMISSION	✆ LABELING REVISION
✆ DRUG ADVERTISING	✆ SAFETY/EFFICACY	✆ ORIGINAL NEW CORRESPONDENCE
✆ ADVERSE REACTION REPORT	✆ PAPER NDA	✆ FORMULATIVE REVIEW
✆ MANUFACTURING CHANGE/ADDITION	✆ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
✆ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW	✆ CHEMISTRY
✆ END QF PHASE II MEETING	✆ PHARMACOLOGY
✆ CONTROLLED STUDI ES	✆ BIOPHARMACEUTICS
✆ PROTOCOL REVIEW	✆ OTHER
✆ OTHER	

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

Requesting consult for inactive ingredient Oleic Acid. Firm has proposed to use (b) in a topical product. This is greater than used in a previously approved drug product. Firm has submitted pharmacology and toxicology information available in EDR dated 1/9/07.Please cc Benjamin Danso, HFD-617 (benjamin.danso@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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

/s/

Benjamin Danso
1/29/2007 11:15:20 AM
OGD CONSULT FOR ANDA 78-548.

Pharma

ALTANA

Notice of non-litigation within 45 day time period.

March 19, 2007

Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855

ORIGINAL
N-000-XP

ALTANA Inc
60 Baylis Road
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Melville, NY 11747-0103
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www.altanainc.com

VIA TELEFAX AND FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

COMPUTATION OF 45-DAY TIME CLOCK

Reference is also made to ALTANA's January 17, 2007 Amendment providing documentation of notification/receipt of notice by the patent owner or its representative and the NDA holder. In accordance with 21 CFR 314.107(f), the last day of the 45-day clock was March 2, 2007.

NO LEGAL ACTION TAKEN

This Patent Amendment is being submitted to confirm that as of the date of this letter, which is beyond the expiration of the 45-day period, ALTANA Inc has NOT been notified of legal action for patent infringement by either the NDA or patent holder.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

MAR 20 2007
OGD / CDER

RJA:tl

\\usbfs41\users\Regulatory\Shared\Imiquimod Cream 5%\Amendments\Patent\Documentation of Litigation-Settlement Outcome 3-19-07.rtf

MINOR AMENDMENT

ANDA 78-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Altana, Inc. TEL: 631-454-7677

ATTN: Robert J. Anderson FAX: 631-756-5114

FROM: Rosalyn Adigun PROJECT MANAGER: (301)-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream, 0.5%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
See Chemistry comments provided

Following this page, 2 pages withheld in full - (b)(4)

5. The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

{See appended electronic signature page}

Rasmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Paul Schwartz
3/20/2007 04:16:15 PM
Signed for R. Patel

ORIGINAL

Pharma

ALTANA

March 30, 2007

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ORIG AMENDMENT
N-000-AM

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
APR 0 3 2007
OGD / CDER

VIA FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream, 5%
MINOR AMENDMENT – RESPONSE TO CHEMISTRY DEFICIENCIES

Dear Dr. Patel:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream, 5%.

ALTANA Inc acknowledges the FDA correspondence dated March 20, 2007, citing Chemistry Deficiencies.

This correspondence has been identified as a MINOR AMENDMENT. Each item has been addressed in **comment** / response format.

A. Deficiencies:

1. Please provide a [redacted] (b) (4)

[redacted] (b) (4)

The revised [redacted] (b) (4) are included as **Attachment I.** The revised ALTANA [redacted] (b) (4) specifications are included as **Attachment II.**

Following this page, 2 pages withheld in full - (b)(4)

9. **Please provide** (b) (4) **drug product IMIQUIMOD Cream 5%.**

(b) (4)

and found to be satisfactory.

The results are included as **Attachment IX**.

10. **Please revise your** (b) (4)

(b) (4)

as **Attachment X**.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **Please refer to the telephone conference between the agency and ALTANA Inc. that occurred on March 13, 2007 regarding the calculation of the maximum daily dosage (MDD) of your drug product. Please revise and correct the MDD calculations in all applicable sections of your application.**

   Based on the teleconference between the agency and ALTANA Inc representatives held on March 13, 2007, the Maximum Daily Dose (MDD) has been recalculated. Revised MDD calculations for all applicable sections of the application are included as **Attachment XI**.

2. **The firms referenced in your application should be in compliance with CGMP at the time of approval.**

   ALTANA acknowledges that firms referenced in the application should be in compliance with CGMP at the time of approval.

3. **Please provide all available drug product stability data.**

   All available long-term drug product Stability data for the presentations for which ALTANA is seeking approval are provided as **Attachment XII**.

4. **The bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.**

   ALTANA acknowledges that bioequivalence information is under review and that any deficiencies found will be communicated to ALTANA under separate cover.

5. **The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.**

   ALTANA acknowledges that labeling information is under review and that any deficiencies found will be communicated to ALTANA under separate cover.

To aid the reviewer, a copy of this Amendment response letter has been included on CD-ROM in MS-Word format.

If you have any questions, or require additional information, please contact Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677, ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA Inc

Amy M Byrom /for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RJA:tl

Pharma

ALTANA

ORIG AMENDMENT

April 27, 2007

N/AM

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Dale P. Conner, Pharm.D
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA TELEFAX (240) 276-8966 and FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT-REQUEST FOR INFORMATION

Dear Dr. Conner:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on April 26, 2007 between FDA and ALTANA representatives in which FDA requested additional information.

This correspondence has been identified as a **TELEPHONE AMENDMENT-REQUEST FOR INFORMATION**. Each item has been addressed in **comment** / response format.

1. **Provide an updated investigator list that includes the actual number of patients at each site.**

   Attachment I contains a tabular listing of the actual number of patients at each investigator site. An updated site contact list for the investigators has also been included.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RECEIVED
APR 30 2007
OGD / CDER

Pharma

ALTANA

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May 30, 2007

MC

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA TELEFAX AND FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – RESPONSE TO REQUEST FOR INFORMATION

Dear Dr. Patel:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on May 25, 2007 between FDA and ALTANA representatives in which FDA requested additional information.

This correspondence has been identified as a TELEPHONE AMENDMENT – RESPONSE TO REQUEST FOR INFORMATION. Each item has been addressed in **comment** / response format.

1. **Please provide information regarding the [redacted] (b) (4) used to manufacture Imiquimod Cream 5%.**

   A copy of the Certificate of Analysis included in the original ANDA submission has been provided in **Attachment I**. The product name specifies NF grade. ALTANA has obtained a statement from the manufacturer, [redacted] (b) (4) which indicates the [redacted] (b) (4) used in the manufacture of Imiquimod Cream 5% was manufactured with materials of [redacted] (b) (4) origin and was NF grade. A copy of this statement and the manufacturer's current specification, which includes a note about the material's origin, are also included in **Attachment I.**

RECEIVED

MAY 31 2007

OGD

If you have any questions, or require additional information, please contact Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677, ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA Inc

Audrey Zaweski for

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RJA:tl

Pharma

ORIG AMENDMENT

ALTANA

N/AM

May 11, 2007

ALTANA Inc
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Dale P. Conner, Pharm.D
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA TELEFAX (240) 276-8966 and FEDERAL EXPRESS

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT-REQUEST FOR INFORMATION

Dear Dr. Conner:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on April 26, 2007 between FDA and ALTANA representatives in which FDA requested additional information. The ALTANA response dated April 27, 2007 included an updated site contact list for the investigators. Address information for site #4, Dr. Terry Jones, site #10, Dr. Shari Skinner and site #11, Dr. Solomon has subsequently been updated. In addition, contact information for site #11, Dr. Solomon and site #16, Dr. Bruce has also been revised. An updated site contact list for the investigators is included as **Attachment I.**

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677, extension 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

for/ Audrey Zaweski

Robert J. Anderson, Esq.
Vice President, Scientific Affairs

RECEIVED
MAY 14 2007
OGD

RJA:dt

MINOR AMENDMENT

ANDA 78-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Altana, Inc. TEL: 631-454-7677

ATTN: Robert J. Anderson FAX: 631-756-5114

FROM: Rosalyn Adigun PROJECT MANAGER: (301)-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 16, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream, 0.5%.

Reference is also made to your amendments dated March 30, 2007 and May 11, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

See Chemistry comments provided

Following this page, 2 pages withheld in full - (b)(4)

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

/s/

Paul Schwartz
7/30/2007 05:32:00 PM
Signed for R. Patel

October 2, 2007

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA ELECTRONIC SUBMISSIONS GATEWAY

ANDA 78-548
Imiquimod Cream, 5%
MINOR AMENDMENT – RESPONSE TO CHEMISTRY DEFICIENCIES

Dear Dr. Patel:

Reference is made to the ALTANA Inc Abbreviated New Drug Application dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream, 5%.

ALTANA Inc acknowledges the FDA correspondence dated July 30, 2007, citing Chemistry Deficiencies.

This correspondence has been identified as a MINOR AMENDMENT. Each item has been addressed in **comment** / response format.

A. Deficiencies:

1. Please provide an additional [redacted] (b) (4)

Additional [redacted] (b) (4) information for the [redacted] (b) (4) is summarized as follows:

Following this page, 7 pages withheld in full - (b)(4)

[redacted]:

- [redacted]
- [redacted]

An investigation is ongoing to determine the [redacted] results, including:

- Review of the [redacted] 2) evaluate [redacted] procedures and (3) evaluate the effect of [redacted]
- Optimization of the [redacted] process
- Batch record review

The results of this investigation will be provided when available.

The summary table included on page 1637 of the original ANDA submission has been revised to include the component part numbers for the two [redacted] foilpacs used in the manufacture of Lot #W346. A copy of the revised page is included in this submission.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
ALTANA Inc

Audrey Zaweski — 02/Oct/2007 02:00 PM

For *Vice President,* Scientific Affairs — Date

RJA:tl

Telephone Fax

ANDA 78-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240- 276-8984

TO: Altana, Inc.

TEL: 631 454-7677 ext. 3007

ATTN: Audrey Zaweski

FAX: 631 756-5114

FROM: Beverly Weitzman

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream 5%

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-548

Date of Submission: October 16, 2006

Applicant's Name: Altana

Established Name: Imiquimod Cream, 5%

Labeling Deficiencies:

1. **CONTAINER (Single foil Packet):**
   - Add the statement "**Discard unused** (b) (4)".
   - If space permits, you may add the route of administration and storage statement as does the reference listed drug, Aldara.
2. **CARTON (12 single-use packets):**
   - Revise your storage temperature to read as "Store at 4 - 25°C (39 - 77°F)".
   - Replace "(b) (4)" with the statements "For Dermatologic Use Only" and "Not for Ophthalmic Use".
   - Revise "(b) (4) ingredients" to read as "inactive ingredients'
   - Recommend adding the statement "This package is not child resistant"
3. **INSERT:** Revise your package insert labeling to be in accord with the most recently approved labeling for the reference listed drug, Aldara (NDA 20-723/S-020: Approved March 22, 2007). We refer you to http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
4. **PATIENT INFORMATION:** See INSERT Comment.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug insert labeling and a side-by-side comparison of your proposed carton and container labels with your last submission, with all differences annotated and explained

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
1/10/2008 12:47:10 PM
for Wm Peter Rickman

January 22, 2008

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA ELECTRONIC SUBMISSIONS GATEWAY

ANDA 78-548
Imiquimod Cream, 5%
LABELING AMENDMENT
COMPANY NAME CHANGE

Dear Mr. Rickman:

Reference is made to the ALTANA Inc Abbreviated New Drug Application submitted on October 16, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

ALTANA acknowledges the FDA correspondence dated January 10, 2008 citing labeling deficiencies. Each item has been addressed in **comment** / response format.

In addition, please be advised that as of September 24, 2007 the corporate name has been changed from ALTANA Inc to Nycomed US Inc. This does not reflect a change in the US corporate entity.

The site of manufacture, controls and personnel remain the same. Nycomed US Inc. will continue to adhere to all provisions provided for in the referenced Abbreviated New Drug Application.

All Final Printed Labeling has been revised to reflect the company name change as well as the FDA comments. A copy of the revised container, carton and package insert are included in this submission.

Labeling Deficiencies:

1. **CONTAINER (Single foil Packet):**

- **Add the statement "Discard unused (b) (4)".**

  Nycomed US Inc. has revised the container label to include the statement "Discard Unused Portion" as agreed at the teleconference held between FDA and Nycomed US Inc. representatives on January 18, 2008.

- **If space permits, you may add the route of administration and storage statement as does the reference listed drug, Aldara.**

  Nycomed US Inc. has revised the container label to include the route of administration and storage statement.

2. **CARTON (12 single-use packets):**

- **Revise your storage temperature to read as "Store at 4 – 25ºC (39 – 77ºF)".**

  Nycomed US Inc. has revised the storage statement on carton labeling to read as "Store at 4 – 25ºC (39 – 77ºF)".

- **Replace "(b) (4)" with the statements "For Dermatologic Use Only" and "Not for Ophthalmic Use".**

  Nycomed US Inc. has revised the carton labeling to replace (b) (4)" with the statements "For Dermatologic Use Only" and "Not for Ophthalmic Use".

- **Revise "(b) (4) ingredients" to read as "inactive ingredients".**

  Nycomed US Inc. has revised the carton labeling to change "(b) (4) ingredients" to read as "inactive ingredients".

- **Recommend adding the statement "This package is not child resistant".**

  Nycomed US Inc. has revised the carton labeling to include the statement "This package is not child resistant".

  In addition, Nycomed US Inc. has revised the carton label to include the statement "Discard Unused Packets" as agreed at the teleconference held between FDA and Nycomed US Inc. representatives on January 18, 2008.

3. **INSERT: Revise your package insert labeling to be in accord with the most recently approved labeling for the reference listed drug, Aldara (NDA 20-723/S-020: Approved March 22, 2007). We refer you to http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.**

   Nycomed US Inc. has revised the package insert labeling to be in accord with the most recently approved labeling for the reference listed drug, Aldara (NDA 20-723/S-020: Approved March 22, 2007).

4. **PATIENT INFORMATION: See INSERT Comment.**

   Nycomed US Inc. has revised the patient information labeling to be in accord with the most recently approved labeling for the reference listed drug, Aldara (NDA 20-723/S-020: Approved March 22, 2007).

Revise your labeling, as instructed above, and submit final printed labeling electronically. Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address – http://service.govdelivery.com/service/subscribe.html?code=USFDA 17.

Nycomed US Inc. acknowledges that prior to approval it may be necessary to further revise the labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, Nycomed US Inc. will subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address – **http://service.govdelivery.com/service/subscribe.html?code=USFDA 17.**

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug insert labeling and a side-by-side comparison of your proposed carton and container labels with your last submission, with all differences annotated and explained.

In order to facilitate review of this submission, a side-by-side comparison of the Nycomed US Inc. proposed labeling with the reference listed drug insert labeling has been provided as well as a side-by-side comparison of the Nycomed Us Inc. proposed carton and container labels with our last submission, with all differences annotated and explained.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

NYCOMED US Inc.

Katherine M. McNeal

22/Jan/2008 12:49 PM

For Robert J. Anderson, Esq.
Vice President, Scientific Affairs

February 13, 2008

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream, 5%
LABELING AMENDMENT-ADDITIONAL INFORMATION TO SUPPORT JANUARY 22, 2008 LABELING AMENDMENT

Dear Mr. Rickman:

Reference is made to the Nycomed US Inc. Abbreviated New Drug Application submitted on October 16, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the FDA teleconference held on February 12, 2008 between FDA and Nycomed US Inc. representatives in which FDA requested that the patient information be reformatted into a stand-alone document.

Nycomed US Inc. has revised the patient information as requested and a copy is included in this submission.

As per the FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format-Content of Labeling", the professional package insert and patient information were included in xml format in the labeling submission dated January 22, 2008. Since the content of the patient information has not changed the xml previously submitted is still current.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

NYCOMED US Inc.

Audrey Zaweski

13/Feb/2008 03:41 PM

For Robert J. Anderson, Esq.
Vice President, Scientific Affairs

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 78-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Altana, Inc.

TEL: 631-454-7677 ext. 3007

ATTN: Audrey Zaweski

FAX: 631-756-5114

FROM: Debra Catterson

PROJECT MANAGER: (240) 276-8963
(240) 276-8966 (fax)

Dear Madam:

This facsimile is a request for information from the Clinical Review Team, regarding your ANDA 78-548 for Imiquimod Cream, 5%.

The information request is presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 78-548

To: **Altana, Inc.**

Drug: **Imiquimod Cream, 5%**

From: **Carol Y. Kim, PharmD**
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

Date: **March 19, 2008**

Re: **Request for Information**

In order to complete the review of a bioequivalence study with a clinical endpoint for ANDA 78-548 (#ALT 0432-01-01), please submit the following information:

1. A copy of Case Report Forms (CRF) for the following patients:

   Test: site 10/#518, 527; 13/192, 201, 786
   Reference: site 2/#360; 7/304; 9/4, 5, 6; 10/469, 476, 509; 11/254; 16/745, 753
   Vehicle: site 9/#858

2. A copy of the IRB approval letter for protocol and an informed consent form.

3. Manufacturing date of the test product and an expiration date of the reference product.

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

/s/

Dena Hixon

3/20/2008 10:38:18 AM

March 28, 2008

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA ELECTRONIC SUBMISSIONS GATEWAY

ANDA 78-548
Imiquimod Cream 5%
BIOEQUIVALENCY AMENDMENT-RESPONSE TO REQUEST FOR INFORMATION

Dear Dr. Hixon:

Reference is made to the Nycomed US Inc. Abbreviated New Drug Application submitted on October 16, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Nycomed US Inc. acknowledges the FDA correspondence dated March 19, 2008 requesting Bioequivalency information.

This correspondence has been identified as a BIOEQUIVALENCY AMENDMENT-RESPONSE TO REQUEST FOR INFORMATION. Each item has been addressed in **comment** / response format.

In order to complete the review of a bioequivalence study with a clinical endpoint for ANDA 78-548 (#ALT 0432-01-01), please submit the following information:

1. **A copy of Case Report Forms (CRF) for the following patients:**

   Test: site 10/#518, 527; 13/192, 201, 786
   Reference: site 2/#360; 7/304; 9/4, 5, 6; 10/469, 476, 509; 11/254; 16/745, 753
   Vehicle: site 9/#858

   Copies of the following Case Report Forms are included in this submission:

Site Number	Patient ID Number
2	360
7	304
9	4, 5, 6 and 858
10	469, 476, 509, 518 and 527
11	254
13	192, 201 and 786
16	745 and 753

2. **A copy of the IRB approval letter for protocol and an informed consent form.**

   The IRB approved the initial protocol, informed consent and Amendment 1 via individual approval letters to each site. An example of this approval letter and the informed consent form are included in this submission. The IRB approval of Amendment 2 was issued December 2, 2005 as a single letter covering all sites. A copy of the IRB approval letter for Amendment 2 is included in this submission.

3. **Manufacturing date of the test product and an expiration date of the reference product.**

   The test product Lot T045 was manufactured on June 29, 2005 and the reference product Lot FG036A expired in July 2006.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,

Nycomed US Inc.

Audrey Zaweski — 28/Mar/2008 04:57 PM

For *Vice President*, Scientific Affairs — Date

June 12, 2008

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream, 5%
GRATUITOUS AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream, 5%.

Reference is also made to Nycomed's Minor Amendment dated October 2, 2007.

Nycomed is submitting this Gratuitous Amendment to :

- Request approval for (b) (4) included in the original ANDA submission
- Provide an update on the investigation of (b) (4) results

Stability data for both foilpacs (b) (4) are acceptable under long-term controlled room temperature storage conditions. All long-term stability results at 25°C±2°C/60%RH±5%RH are within specification and support a 24-month expiration date.

Background

The original ANDA submission included two exhibit batches, lots T045 and W346. These batches were filled in multiple container/closure systems as summarized below:

Following this page, 1 page withheld in full - (b)(4)

- Revised the analytical procedure
  - (b) (4)
  -
- Added a comparison of the (b) (4) to manufacturing.

A copy of the revised Drug Product Analytical Procedure is included in this submission.

Updated stability data for foilpac (b) (4) are also included in this submission.

The stability data for both foilpacs (b) (4) and (b) (4) under long-term controlled room temperature storage conditions support a 24-month expiration date.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Amy M. Byrom
For Robert J. Anderson, Esq.
Vice President, Scientific Affairs

12/Jun/2008 01:08 PM
Date

July 24, 2008

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is made to the telephone conversation between FDA and Nycomed representatives on July 24, 2008 in which FDA requested information on residual solvents.

This correspondence has been identified as a TELEPHONE AMENDMENT – CHEMISTRY.

In order to comply with the changes to chapter <467> on residual solvents in the current US Pharmacopoeia (USP), which became effective July 1, 2008, Nycomed has revised its specifications for residual solvents for the following drug substance and excipients in Imiquimod Cream 5%:

API / Excipient	Nycomed Item Number
Imiquimod	(b) (4)
Oleic Acid NF	
Benzyl Alcohol NF	
Polysorbate 60 NF	
Sorbitan Monostearate NF	
Cetyl Alcohol NF	
Stearyl Alcohol NF	
White Petrolatum USP	
Propylparaben NF	
Purified Water USP	
Glycerin USP	
Methylparaben NF	
Xanthan Gum NF	

The revised specifications are included in this submission. (b) (4)

(b) (4)

Nycomed commits to reassess its compliance with USP <467> if it changes ingredient suppliers in the post approval period including implementing revised controls, if appropriate.

If you have any questions, please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Amy M. Byrom — 24/Jul/2008 04:49 PM

For Robert J. Anderson, Esq.
Vice President, Scientific Affairs — Date

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

August 15, 2008

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the telephone conversation between FDA and Nycomed representatives on July 30, 2008 in which FDA requested additional information on residual solvents.

This correspondence has been identified as a TELEPHONE AMENDMENT – CHEMISTRY. Each item has been addressed in **comment** / response format.

1. **Provide copies of** (b) (4)

   A. (b) (4)
   B.
   C.
   D.
   E.

(b) (4)

(b) (4)

2.

3.

If you have any questions, please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Audrey Zaweski — 15/Aug/2008 01:35 PM

For Robert J. Anderson, Esq.
Vice President, Scientific Affairs — Date

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

August 22 2008

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA ELECTRONIC SUBMISSIONS GATEWAY

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the telephone conversation between FDA and Nycomed representatives on August 18, 2008 in which FDA requested additional information.

This correspondence has been identified as a TELEPHONE AMENDMENT – CHEMISTRY. Each item has been addressed in **comment** / response format.

1. **Provide a copy of representative** (b) (4) [redacted].

   Representative (b) (4) [redacted] are included in this submission.

If you have any questions, please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Amy M. Byrom
For Robert J. Anderson, Esq.
Vice President, Scientific Affairs

22/Aug/2008 03:01 PM
Date

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

August 28, 2008

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") dated October 16, 2006 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the telephone conversation between FDA and Nycomed representatives on August 27, 2008 in which FDA requested additional information for residual solvents.

This correspondence has been identified as a TELEPHONE AMENDMENT – CHEMISTRY and has been prepared in **comment /** response format.

1. (b) (4)

2.

3.

4.

In accordance with the additional information provided by the Office of Generic Drugs (OGD) regarding implementation of USP <467> which states, "Applications otherwise acceptable for Tentative Approval may be granted Tentative Approval status if there is a commitment to demonstrate compliance prior to final approval." Nycomed has submitted a substantially complete ANDA for Imiquimod Cream 5% and commits to demonstrate compliance with USP <467> prior to final approval. The items identified by OGD in this correspondence will be addressed by Nycomed prior to final approval of the application. Therefore, at this time Nycomed respectfully requests Tentative Approval for this application.

If you have any questions, please contact Ms. Audrey Zaweski, *Director*, Regulatory Affairs, at (631) 454-7677 ext. 3007. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Audrey Zaweski — 28/Aug/2008 02:40 PM

For Robert J. Anderson, Esq.
Vice President, Scientific Affairs — Date

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2007-0102**	
TO *(Division/Office)* DDOP - HFD-150 Thru: Frank Cross, OODP HFD-106			FROM: Iain Margand	
DATE: 1/26/2009	IND NO.	~TYPE~ NO. 078548	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 1/8/2007
NAME OF DRUG Imiquimod Cream		PRIORITY CONSIDERATION 15 days	CLASSIFICATION OF DRUG topical treatment for basal cell carcinoma	DESIRED COMPLETION DATE 2/13/2009
NAME OF FIRM Altana Inc.				

REASON FOR REQUEST

I. GENERAL

✆ NEW PROTOCOL	✆ PRE NDA MEETING	✆ RESPONSE TO DEFICPENCY LETTER
✆ PROGRESS REPORT	✆ END OF PHASE II MEETING	✆ FINAL PRINTED LABELING
✆ NEW CORRESPONDENCE	✆ RESUBMISSION	✆ LABELING REVISION
✆ DRUG ADVERTISING	✆ SAFETY/EFFICACY	✆ ORIGINAL NEW CORRESPONDENCE
✆ ADVERSE REACTION REPORT	✆ PAPER NDA	✆ FORMULATIVE REVIEW
✆ MANUFACTURING CHANGE/ADDITION	✆ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
✆ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW	✆ CHEMISTRY
✆ END QF PHASE II MEETING	✆ PHARMACOLOGY
✆ CONTROLLED STUDI ES	✆ BIOPHARMACEUTICS
✆ PROTOCOL REVIEW	✆ OTHER
✆ OTHER	

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

Requesting consult for inactive ingredient Oleic Acid. Firm has proposed to use (b) in a topical product. This is greater than used in a previously approved drug product. Firm has submitted pharmacology and toxicology information available in EDR dated 1/9/07.Please cc Theresa Liu, HFD-617 (theresa.liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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

/s/

Theresa Liu

1/26/2009 09:22:55 AM

March 13, 2009

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA ELECTRONIC SUBMISSIONS GATEWAY

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") accepted for filing on October 17, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the telephone conversation between the FDA Chemistry Reviewer and Nycomed's Manager of Regulatory Affairs on March 13, 2009 in which FDA requested additional information on residual solvents.

As stated in Nycomed's August 28, 2008 response to the last Office of Generic Drugs ("OGD") Telephone Amendment dated August 27, 2008, Nycomed has committed to demonstrate compliance with USP <467> prior to final approval. This commitment was made in accordance with OGD guidance regarding implementation of USP <467> which states, "Applications otherwise acceptable for Tentative Approval may be granted Tentative Approval status if there is a commitment to demonstrate compliance prior to final approval."

The only outstanding items identified in OGD's August 28, 2008 Telephone Amendment were related to residual solvents. Therefore, Nycomed's ANDA for Imiquimod Cream 5% is a substantially complete ANDA for Tentative Approval prior to the expiration of the 30-month review[1] on April 17, 2009.

Nevertheless, to facilitate issuance of the Tentative Approval, Nycomed has been addressed each item requested in the March 13, 2009 Telephone Amendment in **comment** / response format.

1. (b) (4)

[1]As required by 21 U.S.C.§ 355(j)(5)(D)(i)(IV)

(b) (4)
residual solvents is included in this submission.

2. **For** (b) (4) **residual solvents.**

(b) (4)
residual solvents are included in this submission.

3. **Revise the** (b) (4)

(b) (4)

If you have any questions or require additional information, please contact Ms. Amy Byrom, *Manager*, Regulatory Affairs, at (631) 719-2098. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Amy M. Byrom 13/Mar/2009 05:15 PM

For Robert J. Anderson, Esq. Date
Vice President, Scientific Affairs

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Susan Walker, M.D.
Director
Division of Dermatology and Dental Products (DDDP)

FROM:
Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 13, 2009		78-548		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Imiquimod Cream, 5%		Immune response modifier	April 13, 2009

NAME OF FIRM: TEVA

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Office of Generic Drugs (OGD) is preparing to post bioequivalence recommendations on the FDA Guidance for Industry Webpage for generic versions of imiquimod cream, 5% (reference listed drug, Aldara™ cream, 5%). We are requesting comments from DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses (AK). Please see attachment for draft BE recommendations.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) x MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

REQUEST FOR CONSULTATION

To: **Susan Walker, M.D.**
Director
Division of Dermatology and Dental Products (DDDP)
HFD-540

From: **Carol Y. Kim, Pharm.D.**
Clinical Reviewer
Office of Generic Drugs

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Re **Bioequivalence (BE) study recommendations for imiquimod cream 5%**

Date of Request **March 13, 2009**
Date Response Requested **April 13, 2009**

Reason for Consultation

The Office of Generic Drugs (OGD) is preparing to post bioequivalence recommendations on the FDA Guidance for Industry Webpage for generic versions of imiquimod cream, 5% (reference listed drug, Aldara™ cream, 5%). Please see the attached draft BE recommendations. We are requesting comments from DDDP regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study in the treatment of Actinic Keratoses (AK).

Background

Imiquimod is an immune response modifier that is approved for the treatment of three indications:

1) Treatment of external genital and perianal warts/condyloma acuminata in patients 12 years old or older
2) Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
3) Topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.

All three of the approved indications arise in the epidermis of the skin. OGD believes that the same considerations apply to bioequivalence determinations for this drug product as for 5% 5-fluourouracil cream, which has two of the same indications (AK and sBCC)

and was previously considered in detail. Given that these recommendations were upheld at upper levels of CDER management and in a subsequent court decision, we believe that the same general recommendations are also appropriate for generic imiquimod cream products.

Treatment of external genital and perianal warts/condyloma acuminata in patients 12 years old or older

NDA 20-723 was originally approved by HFD-530, the Division of Anti-Viral Products (DAVP) on 2/27/97 for the treatment of external genital and perianal warts/condyloma acuminata in patients at least 12 years of age. The recommended treatment regimen is 3 times per week applications for a maximum of 16 weeks, stopping at the time of complete clearance. The rate of complete clearance in the NDA studies was 50% for 5% Aldara cream (72% for females, and 33% for males), vs. 21% with 1% Aldara cream, and 11% with vehicle. The median time to complete clearance was 10 weeks with 5% Aldara and 12 weeks with vehicle. A follow-up visit was conducted 12 weeks after the end of treatment to evaluate for recurrence.

Imiquimod has no direct antiviral activity in cell culture. According to the approved labeling, Aldara™ Cream induces mRNA encoding cytokines including interferon-α at the treatment site in patients treated for external genital/perianal warts.

Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults

NDA 20-723/S-015 was approved on 5/1/03 by HFD-540, the Division of Dermatology and Dental Products (DDDP) for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults. The recommended treatment regimen is twice weekly applications for 16 weeks, with treatment evaluation at 8 weeks after the end of treatment. The rate of complete clearance of AK was 44% to 46% in the Aldara™ group and 3% to 4% in the vehicle group.

The mechanism of action of Aldara™ cream for topical treatment of AK lesions and sBCC is unknown. The approved labeling suggests that imiquimod increases baseline biomarker levels for CD3, CD4, CD8, CD11c, and CD68 in patients treated for Actinic Keratoses. However, the clinical relevance of these findings is unknown.

Topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured

NDA 20-723/S-016 was approved on 7/14/04 by HFD 540 for the topical treatment of primary superficial basal cell carcinoma (sBCC) in immunocompetent adults. The labeling states that the histological diagnosis of superficial basal cell carcinoma should be

established prior to treatment, since safety and efficacy of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular and morpheaform (fibrosing or sclerosing) types. The recommended treatment regimen is 5 times per week applications for 6 weeks, with treatment evaluation at 12 weeks after the end of treatment. The complete clearance rates were 70% to 80% in the Aldara™ group and 1% to 2% in the vehicle group.

The clinical observations in patients treated for sBCC show a local immune-mediated response at the site of application that is similar to classic cell-mediated immune reactions in the skin. Two clinical studies demonstrated that Aldara™ Cream stimulates the infiltration of tumor-destructive cells (T-cell lymphocytes, dendritic cells, and macrophages) into the basal cell carcinoma lesion and reduces the defense mechanisms of tumor.

Generic considerations

For a generic product to be approved, the sponsor must show that it contains the same active ingredient in the same amount as the reference listed drug (RLD) and that it is bioequivalent to the RLD (becomes available at the site of action at the same rate and extent). Inactive ingredients may be different than those contained in the RLD as long as the ingredients used have previously been used in at least the same amount in another drug product for the same route of administration and the change in inactive ingredients will not affect the safety or effectiveness of the product.

For drug products that are administered systemically, bioequivalence of the generic drug to the RLD is demonstrated by pharmacokinetic (PK) studies. However, when the drug product is not intended for systemic absorption, pharmacokinetic studies generally are not reliable for establishing bioequivalence, and a bioequivalence study with clinical endpoints is necessary.

To meet the bioequivalence criteria, the clinical endpoint study should demonstrate that the 90% confidence interval of the difference in success/cure proportions between the test and reference products should be within the limits of (-0.20 to +0.20). The test/reference ratio of means must be within (0.8 to 1.25) for a continuous endpoint. In addition, both the test and reference products should be superior to the placebo ($p<0.05$) with regard to the primary endpoint in order to demonstrate that the test and reference products are active and the study is sufficiently sensitive to detect differences between products. This is especially important when studying a disease such as AK, in which spontaneous resolution may occur.

Multiple treatment indications

When the reference drug product is approved for more than one indication with the same site of pharmacologic activity, bioequivalence is generally established with a single study in the indication that is most likely to discern differences between the generic and reference products. If the product is determined to be bioequivalent for that indication, it is also considered bioequivalent for other indications with the same site of action.

Spear Pharmaceuticals' generic version of 5-fluorouracil (FU) cream, 5%, ANDA 77-524, was approved by the FDA with a single bioequivalence study in the treatment of actinic keratoses. The product is approved for the treatment of multiple actinic or solar keratoses. It is also approved in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. OGD recommended a single bioequivalence study in the treatment of AK to establish bioequivalence. An additional study in the treatment of sBCC was not requested. This recommendation was upheld in the FDA response to a Citizen Petition submitted by Valeant Pharmaceuticals International and in a subsequent court decision.

Systemic Exposure
The labeling of imiquimod cream suggests that systemic absorption is very low with topical administration for the approved indications. As for topically-applied 5-fluorouracil, there are no serious dose-related adverse events known to be related to systemic exposure from the topically-applied product. Therefore, pharmacokinetic bioequivalence studies are not requested.

Discussion
All three indications for imiquimod have a site of action in the epidermis of the skin below the stratum corneum. The presumed mode of action (immune response modifier) is also similar for all three indications. Therefore, a single bioequivalence study with a clinical endpoint using the most discriminatory treatment indication is recommended to establish bioequivalence between the generic and reference products.

The most sensitive clinical endpoint bioequivalence study design is generally conducted in an indication with the least inherent variability, using the lowest recommended treatment dose and/or duration, and the earliest evaluation time at which a significant treatment effect is expected. The indication that is most discriminatory is often one with a lower success rate, as long as the inherent variability in the disease process will not result in a greater variability in the treatment response. An indication with a very high success rate is likely to show similar treatment response even when the products are relatively dissimilar.

For a bioequivalence study with clinical endpoints, the duration of the treatment period and the number of doses received should be the same for all patients, and the study endpoint should be evaluated within a pre-specified visit window.

The AK indication involves uniform treatment of all patients for the same duration with the primary endpoint at 8 weeks after the end of treatment. The clinical diagnosis is straightforward, and the treatment site is readily accessible for application of study drug and evaluation of treatment response. No differences have been described in success rates for different patient populations. The success rate is somewhat lower than that of the other two approved indications. Therefore, this indication is likely to be the most sensitive in detecting a difference between the test and reference products.

These recommendations have been provided to a number of generic sponsors in response to controlled correspondences. OGD has a pending application (ANDA 78-548) for a generic version of this product, with a clinical endpoint bioequivalence study conducted according to these recommendations. The application is acceptable for approval from a regulatory and CMC perspective, and OGD requests your comments on the recommendations before taking an action on this application or posting the recommendations on the FDA internet.

Please feel free to contact us directly to further discuss these issues.

_____

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs
(240) 276-8958

_____

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs
(240) 276-8961

Following this page, 5 pages withheld in full - (b)(5) Draft Guidance

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/s/

Dena Hixon

3/16/2009 07:14:15 AM

March 17, 2009

Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
GENERAL CORRESPONDENCE

Dear Gary:

Thank you for taking time to speak with me yesterday morning regarding Nycomed's pending Imiquimod Cream ANDA 78-548. Nycomed's application was filed on October 17, 2006 and the 30-month review clock for this ANDA expires on April 17, 2009. As the first company to file a Paragraph IV application, it is critical that FDA issue Tentative Approval prior to April 17 in order for Nycomed to preserve its statutory 180-day exclusivity. Loss of this period of exclusivity will have a profound negative impact on the company.

I understand from our conversation that Valeant's 2004 Citizen Petition and subsequent litigation related to fluorouracil raised questions within FDA which resulted in the Agency's need to review the requirements for approval of Imiquimod Cream after Nycomed's application was filed. I can appreciate the challenges of trying to resolve philosophical differences between the Office of Generic Drugs (OGD) and the Office of New Drugs. In this regard, would it be helpful to your office's efforts to conclude its review and to approve our ANDA if we were to bring these issues to the Office of the Ombudsman? If so, we are prepared to begin such consultations immediately.

In an effort to address any pending issues, Nycomed representatives would like to meet with you and your staff, in person, to discuss these issues in more detail and to agree on steps that Nycomed may take to help OGD issue a Tentative Approval. Nycomed will be available to meet whenever your schedule permits.

Because only a relatively few days remain in the 30-month review time, I respectfully ask that you please call me as soon as possible to discuss the appropriate course of action so that Nycomed may preserve the period of exclusivity allowed by law. I can be reached at (631) 719-2085. I look forward to hearing from you in the very near future.

Sincerely,
Nycomed US Inc.

Robert J. Anderson 17/Mar/2009 02:32 PM

Robert J. Anderson, Esq. Date
Vice President, Scientific Affairs

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April 1, 2009

Gary Buehler
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-600, Metro Park North 4
7519 Standish Place
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
TIME SENSITIVE CONTROLLED CORRESPONDENCE – RETENTION OF 180-DAY EXCLUSIVITY

Dear Mr. Buehler:

Reference is made to the Nycomed US Inc. (Nycomed) Abbreviated New Drug Application (ANDA) for Imiquimod Cream 5% accepted for filing on October 17, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Nycomed is submitting this letter to confirm conversations with the Office of Generic Drugs (OGD) in which OGD said it was reviewing the requirements for approval of Imiquimod Cream after ANDA 78-548 was filed and as a result Nycomed will remain eligible and will not forfeit eligibility for 180-day marketing exclusivity[1] if tentative approval is not granted by April 17, 2009 (30 months after the application was filed). Nycomed further requests that the FDA immediately issue tentative approval for ANDA 78-548.

Filing Background

Nycomed is the first applicant (or among the first applicants) to submit an ANDA with a Paragraph IV certification for Imiquimod Cream 5% as a generic equivalent to the Reference Listed Drug (RLD) Aldara™ Cream (NDA 20-723, held by Graceway Pharmaceuticals). Nycomed's ANDA was accepted for filing on October 17, 2006. The patent holder did not initiate a patent infringement case against Nycomed within the 45-day period established by law. Nycomed will be eligible for 180-day marketing exclusivity as long as FDA issues a tentative approval (due to the pending expiration of another patent for which a Paragraph III certification was filed) within 30 months after the ANDA filing date.

Review History

During the first 12 months of review of ANDA 78-548 FDA made one request for additional chemistry information on July 30, 2007, which Nycomed provided on October 2, 2007. No other communications were received from the Agency during this period. During the next 17 months,

[1] 21 U.S.C. §355 (j)(5)(D)(i)(IV)

FDA appeared to be actively reviewing the ANDA as is evident from the following eight requests for information, all of which Nycomed promptly provided:

Type of Request	FDA Request Date	Nycomed Response Date	Length of Response Time (calendar days)
Labeling	01/10/2008	01/22/2008	12
	02/12/2008	02/13/2008	1
CMC	07/24/2008	07/24/2008	0
	07/30/2008	08/15/2008	16
	08/18/2008	08/22/2008	4
	08/27/2008	08/28/2008	1
	03/13/2009	03/13/2009	0
Bioequivalence	03/19/2008	03/28/2008	9

Legal Background

The Federal Food, Drug, and Cosmetic Act (FDCA), as amended, provides that the first applicant to have filed an ANDA will forfeit its eligibility to receive 180 days of marketing exclusivity if any of five events should occur. The relevant event in this matter is if Nycomed should fail "to obtain tentative approval of its application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed." § 505(j)(5)(D)(i)(IV) of the FDCA; 21 U.S.C. § 355(j)(5)(D)(i)(IV). Neither the FDCA nor regulations promulgated under its authority explain what would constitute "a change in or a review of the requirements for approval imposed after the date on which the application is filed." Nor has FDA published any guidance interpreting this forfeiture criterion.

Discussion with OGD

In a March 16, 2009 telephone conversation between OGD and Nycomed's Vice President of Scientific Affairs, OGD mentioned that Valeant's 2004 Citizen Petition and subsequent litigation related to fluorouracil raised questions within FDA which resulted in the Agency's need to review the requirements for approval of ANDA 78-548 imposed after the date on which the ANDA was filed. Therefore, pursuant to § 505(j)(5)(D)(i)(IV) of the FDCA, forfeiture of Nycomed's eligibility for 180 days of marketing exclusivity would not be triggered for ANDA 78-548 in the event that FDA does not issue a tentative approval by April 17, 2009.

Nycomed's 180-Day Exclusivity Should Be Preserved By All Legal Means Available

Nycomed has worked very closely with OGD over the last 29+ months to answer reviewer questions and respond to additional information requests in a timely manner so that tentative approval would be issued by April 17, 2009. Nycomed has made a significant investment into ANDA 78-548, including development of a non-infringing formulation, conduct of a full clinical endpoint bioequivalence study, and extensive patent analysis. As such, Nycomed will continue to evaluate all possible courses of action, including available legal remedies up to and including filing of legal action, to ensure that its exclusivity is not forfeited.

Nycomed would greatly appreciate FDA's written acknowledgement no later than **April 3, 2009** that its review of the approval requirements for Imiquimod Cream after the filing of ANDA 78-548 would preclude such forfeiture. We will contact you within the next 24 hours to make certain you have received this communication and to ask if you have any questions.

In the meantime, if you have any questions or require additional information, please contact Mr. Robert J. Anderson, *Vice President*, Scientific Affairs, directly at (631) 719-2085. Fax communications may be made to (631) 756-5114.

We appreciate your attention to this very important matter and look forward to a prompt response.

Sincerely,
Nycomed US Inc.

Amy M. Byrom 02/Apr/2009 09:02 AM

For Robert J. Anderson, Esq. Date
Vice President, Scientific Affairs

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Adigun, Rosalyn

From: West, Robert L
Sent: Friday, April 10, 2009 7:04 AM
To: Adigun, Rosalyn
Cc: Ames, Timothy W; Rickman, William P
Subject: FW: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE - NYCOMED IMIQUIMOD CREAM

Rosalyn:

Please file this e-mail in DFS for Nycomed's ANDA 78-548. Title it "Issues - 180-day Forfeiture".

Thanks,

Bob

From: Buehler, Gary J
Sent: Thursday, April 09, 2009 3:28 PM
To: West, Robert L; Read, David T; Shimer, Martin
Cc: Read, David T; Levine, Susan; Catterson, Debra M; Adigun, Rosalyn; Rickman, William P
Subject: RE: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE - NYCOMED IMIQUIMOD CREAM

I agree that this is the case. We recently consulted this application to the derm division to review our BE recommendations. This should qualify as a review of BE recommendations during the review process. I guess we need to vet this with Liz also.

Gary

From: West, Robert L
Sent: Thursday, April 09, 2009 1:23 PM
To: Buehler, Gary J; Read, David T; Shimer, Martin
Cc: Read, David T; Levine, Susan; Catterson, Debra M; Adigun, Rosalyn; Rickman, William P
Subject: RE: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE - NYCOMED IMIQUIMOD CREAM

I received another call from Nycomed today concerning their ANDA 78-548 for Imiquimod Cream. They are concerned about forfeiting their eligibility for 180-day exclusivity for this drug product by not having received a tentative approval letter by April 17th.

It's clear that we will not meet the April 17th goal.

Do we agree that the complexity of the bio review with the additional consult(s) needed (additional agency requirement) can serve as a basis for Nycomed not to loose its eligibility? I believe that all other reviews have been completed and EES is acceptable.

If so, can Dave/Susan formally document our decision in a memorandum to the record?

Thanks,

Bob

From: Buehler, Gary J
Sent: Friday, April 03, 2009 8:50 AM
To: West, Robert L; Read, David T; Parise, Cecelia M; Shimer, Martin
Subject: RE: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE - NYCOMED IMIQUIMOD CREAM

A consult was sent to the Derm Division requesting clarification as to whether our recommendations for bio were acceptable. I consider this a review of the current bio recommendations.

Gary

From: West, Robert L
Sent: Friday, April 03, 2009 8:48 AM
To: Buehler, Gary J; Read, David T; Parise, Cecelia M; Shimer, Martin
Subject: RE: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE - NYCOMED IMIQUIMOD CREAM

My first thoughts are that it is a reasonable request because of the complexity of the clinical/bio review, which remains incomplete at this time. Dena/Debbie can fill us in on that.

Bob

From: Buehler, Gary J
Sent: Friday, April 03, 2009 8:32 AM
To: Read, David T; West, Robert L; Parise, Cecelia M; Shimer, Martin
Subject: FW: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE

We will have to discuss this one.

From: Amy.Byrom@Nycomedus.com [mailto:Amy.Byrom@Nycomedus.com]
Sent: Thursday, April 02, 2009 10:24 AM
To: Buehler, Gary J
Cc: RAnderson@altanainc.com; John.DAngelo@NycomedUS.com; (b) (6)@altanapharma-us.com
Subject: ANDA 78-548 TIME SENSITIVE CONTROLLED CORRESPONDENCE

Dear Gary,

Please find attached a correspondence on Imiquimod Cream 5% regarding Nycomed's eligibility for 180-day exclusivity if tentative approval is not granted by April 17, 2009. This correspondence was submitted to ANDA 78-548 this morning via the electronic submissions gateway.

If you have any questions, please do not hesitate to contact Rob Anderson (b) (6) or 631-719-2085), John D'Angelo (631-719-3009) or me. We look forward to hearing from you shortly.

Best Regards,
Amy

Amy M. Byrom
***Manager,* Regulatory Affairs**

Nycomed US Inc.

60 Baylis Rd
Melville, NY 11747

Office Direct (631) 719-2098
Office General (631) 454-7677, x2098
Blackberry (b) (6)
Fax (631) 756-5114
Email: amy.byrom@nycomedus.com

Attached copy of April 1, 2009, Nycomed letter removed as a duplication.

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/s/

Rosalyn Adigun
4/10/2009 07:21:43 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-548 - Imiquimod Cream 5%

Nycomed US Inc.
Attention: Robert J. Anderson, Esq.
P.O. Box 2006
60 Baylis Road
Melville, NY 11747

SENT VIA FACSIMILE AND US MAIL

Dear Mr. Anderson:

You have pending before the agency an abbreviated new drug application (ANDA) 78-548 for Imiquimod Cream, 5%. By letter of April 1, 2009, you requested that the Office of Generic Drugs inform you whether the Food and Drug Administration (FDA) is reviewing the requirements for approval of ANDAs for Imiquimod Cream, 5%. As you note, under section 505(j)(5)(D)(IV) of the Federal Food, Drug, and Cosmetic Act, the review of the requirements for approval of an application may be a factor in whether an applicant will forfeit eligibility for 180-day exclusivity described in section 505(j)(5)(B)(iv).

This letter confirms that FDA is currently reviewing the approval requirements for ANDAs for Imiquimod Cream, 5%.

If you have any questions, please contact Rosalyn Adigun at 240-276-8518.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Gary Buehler

4/16/2009 03:49:53 PM

M E M O R A N D U M

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

DATE: April 23, 2009

FROM: Martin Shimer
Branch Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-600)

TO: ANDA 78-548

SUBJECT: ANDA status as of the 30-month potential forfeiture date for Nycomed's Imiquimod Cream, 5%

The purpose of this memorandum is to document the status of Nycomed's ANDA 78-548 for Imiquimod Cream, 5%, as of April 17, 2009. This date is significant because Nycomed has failed to receive tentative approval by April 17, 2009 and could therefore forfeit its eligibility for 180-day exclusivity unless the agency determines there was a change in or review of the requirements for approval.

I. FACTUAL BACKGROUND

The following is a timeline of ANDA 78-548:

10/17/06	ANDA submitted (and received for filing) with paragraph IV certification to U.S. Patent number 5,238,944
10/20/06	Firm submitted missing cover letter page
12/6/06	Clinical review team checklist for ANDA completeness
12/21/06	Letter from firm – requested immediate determination of acceptance to file ANDA with a paragraph IV certification
1/10/07	Telephone amendment (cGMP statement for (b) (4) container closure drawing for foilpac, and electronic copies of pharmacology and toxicology information)
1/12/07	Telephone amendment – drug substance and drug product testing
1/18/07	Patent amendment – firm states notice was sent
1/26/07	Oleic Acid consult sent
2/20/07	Firm provided in-vitro data and toxicology summaries to aid reviewers (inactive ingredient oleic acid was not listed in the inactive ingredient guide for a topical cream formulation)
3/20/07	Patent amendment – firm states they were not sued within 45 days; chemistry review (deficient); chemistry deficiencies faxed

4/3/07	Chemistry amendment
5/31/07	Telephone amendment - chemistry
7/30/07	Chemistry review (deficient); chemistry deficiencies faxed
1/10/08	Labeling review (deficient); labeling deficiencies faxed
2/15/08	Labeling review (acceptable)
3/20/08	Bioequivalence request for information
1/30/09	Statistical review
3/16/09	Consult – request comments from DDDP regarding recommended study design and endpoints for a clinical endpoints bio study for the treatment of actinic keratoses
4/16/09	Letter from OGD to Nycomed confirming that FDA is currently reviewing the approval requirements

Nycomed's ANDA was received for filing on October 17, 2006 and has not been tentatively approved as of the date of this memo. The ANDA filing date plus 30 months was April 17, 2009; therefore, Nycomed's ANDA was not tentatively approved within 30 months.

Nycomed submitted a letter to OGD on April 1, 2009 regarding retention of 180-day exclusivity. Their letter noted conversations with OGD in which OGD mentioned reviewing the requirements for approval. OGD sent Nycomed a letter on April 16, 2009 confirming that FDA is currently reviewing the approval requirements for Imiquimod Cream, 5%.

II. STATUTORY AND REGULATORY BACKGROUND

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events which can result in the forfeiture of a first applicant's 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv).

The forfeiture provisions of the MMA now appear at section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act). Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

A "first applicant" is eligible for 180-day exclusivity by virtue of filing a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

"Tentative approval" means, generally, that an ANDA otherwise meets the requirements for approval under the Act, but cannot be fully approved for marketing because of patent or exclusivity protections. Section 505(j)(5)(B)(iv)(II)(dd). The "failure to obtain tentative approval" forfeiture provision establishes a bright line standard: If within 30 months an ANDA has been determined by the agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant maintains eligibility for 180-day exclusivity. If this standard is not met in 30 months, eligibility for 180-day exclusivity is forfeited. It should be noted that the 30 month timeframe generally is without regard to the length of time the ANDA was under review by the Agency. One exception to this general rule, described in section 505(j)(5)(D)(i)(IV), states that forfeiture will not occur if "the failure [to obtain a tentative approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed".

III. DISCUSSION

On March 16, 2009, a request for consultation was sent to the Division of Dermatology and Dental Products (DDDP) to obtain comments regarding the recommended study design and endpoints for a clinical endpoint bioequivalence study for the treatment of Actinic Keratoses. This consult was based, in part, on issues raised during review of ANDAs for Fluorouracil Cream and is considered a review of the requirements for approval.

IV. CONCLUSION

It is FDA's practice to make decisions on eligibility for 180-day exclusivity in the context of specific ANDAs that are otherwise eligible for approval. This approach is necessary because of the many factors that may influence eligibility for exclusivity up to the time an application is ready for approval (e.g., patent expiration, patent delisting, failure to obtain tentative approval within 30 months, withdrawal of ANDA) and could thus render a premature eligibility determination incorrect. As such, FDA will determine whether Nycomed has forfeited eligibility for exclusivity due to failure to obtain tentative approval within 30 months when Nycomed's ANDA is ready for approval or when approval of a subsequent ANDA may be blocked by a first applicant's exclusivity.

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/s/

Martin Shimer
4/23/2009 08:29:15 AM
CSO

July 17, 2009

Gary Buehler
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-600, Metro Park North 4
7519 Standish Place
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
REQUEST FOR MEETING –APPROVAL REQUIREMENTS FOR ANDA 78-548

Dear Mr. Buehler:

Reference is made to the Nycomed US Inc. (Nycomed) Abbreviated New Drug Application (ANDA) 78-548 for Imiquimod Cream 5%, accepted for filing on October 17, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. Nycomed hereby requests an immediate meeting with the Office of Generic Drugs (OGD) to discuss the regulatory review of ANDA 78-548.

Nycomed's ANDA has been under review by OGD since it was filed on October 17, 2006. Nycomed received a letter from OGD on April 16, 2009 confirming that "FDA is currently reviewing the approval requirements for ANDAs for Imiquimod Cream, 5%." To date, Nycomed has not been informed of the specific requirements needed to approve our application.

Nycomed requests a meeting within the next two weeks to discuss the review status of our ANDA and the expected timing of the issuance of the Approval.

We look forward to your prompt reply to this letter. Please do not hesitate to contact me at (631) 719-2085 at any time concerning this matter.

Sincerely,
NYCOMED US, INC.

Amy M. Byrom 17/Jul/2009 01:48 PM

For Robert J. Anderson, Esq.
General Counsel
Vice President, Regulatory Affairs

BIOEQUIVALENCY COMMENTS

ANDA 078548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Nycomed US Inc. TEL: 631-454-7677

ATTN: Robert J. Anderson FAX: 631-756-5114

FROM: Nitin K. Patel PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 16, 2006, April 27, 2007 and March 31, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream, 5%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has provided comments which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078548 APPLICANT: Nycomed US Inc.

DRUG PRODUCT: Imiquimod Cream, 5%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 078548, using the primary endpoint of success (complete clearance of AK lesions) rate in the per protocol population at visit 6/week 24 (8 weeks follow-up), are adequate to demonstrate bioequivalence of Nycomed US Inc.'s Imiquimod 5% Cream, to the reference listed drug (RLD), Graceway Pharmaceuticals' Aldara® Cream, 5%. Both the test and the reference products also demonstrate superiority over vehicle in the modified intent-to-treat population at visit 6, demonstrating that the study is sensitive enough to detect differences between products.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78548	ORIG-1	NYCOMED US INC	IMIQUIMOD

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

/s/

NITIN K PATEL
01/26/2010

DALE P CONNER
01/29/2010

January 20, 2010

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 ***VIA ELECTRONIC SUBMISSIONS GATEWAY***

ANDA 78-548
Imiquimod Cream 5%
TELEPHONE AMENDMENT – CHEMISTRY

Dear Dr. Patel:

Reference is made to the Nycomed US Inc. ("Nycomed") Abbreviated New Drug Application ("ANDA") accepted for filing on October 17, 2006 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Imiquimod Cream 5%.

Reference is also made to the telephone conversation between the FDA Chemistry Team Leader and Nycomed's Manager of Regulatory Affairs on January 20, 2010 in which FDA requested additional information.

Nycomed has addressed each item requested in the January 20, 2010 Telephone Amendment in **comment /** response format.

1. **Provide a single summary sheet of all manufacturers and laboratories and their functions for both drug substance and drug product.**

   A single summary sheet of all manufacturers and laboratories and their functions for both drug substance and drug product is included in this submission. Also included is a list of the addresses and contact information for each site.

2. **Revise the Finished Product specifications to include a specification for Residual Solvents that demonstrates compliance with USP<467> under Option 1.**

   Finished Product specifications have been revised to include a specification for Residual Solvents that demonstrates compliance with USP<467> under Option 1.

If you have any questions or require additional information, please contact Ms. Amy Byrom, *Manager*, Regulatory Affairs, at (631) 719-2098. Fax communications may be made to (631) 756-5114.

Sincerely,
Nycomed US Inc.

Amy M. Byrom 20/Jan/2010 10:35 AM

For Robert J. Anderson, Esq.
General Counsel &
Vice President, Regulatory Affairs

Date

This document has been created and signed electronically in accordance with 21 CFR Part 11. The electronic signatures applied to this document are equivalent to the signer's handwritten signature and are legally binding. The electronic version that is part of the Nycomed US Inc. Document Management System is the original version. Every printed or electronically exported version must be considered a copy.

OGD APPROVAL ROUTING SUMMARY

ANDA # 078548 Applicant Nycomed US Inc.
Drug Imiquimod Cream Strength(s) 5 %

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 28 January 2010 Initials MHS	Date 2/19/10 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Aldara NDA# 20-723
Date Checked Granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 10/17/2006, BOS=Aldara Cream NDA 20-723, PIII cert to '338, PIV to '944. ANDA ack for filing with PIV on 10/17/2006 (LO dated 1/10/2007). Patent Amendment submitted on 1/18/2007-notice sent to 3M in St. Paul MN and delivered on 1/16/2007, notice sent to Graceway Pharmaceuticals in Bristol TN and delivered on 1/16/2007, both notices were sent via the USPS on 1/11/2007. Patent amendment submitted on 3/20/2007-Altana states that suit was not initiated within 45 days.

Altana was the first applicant to submit a substantially complete ANDA which contained a PIV certification to a listed patent((b) (4) actually submitted an ANDA on an earlier date but this ANDA (b) (4) and then WU on (b) (4). Therefore, Altana/Nycomed becames eligible for 180 day exclusivity for this product as their ANDA was filed. Under normal circumstances an applicant must secure TA within 30 months of the submission date which conveys eligibility for 180 day exclusivity. This date would have been 4/17/2009 for this product. That being said, during the pendency of the review of this ANDA the FDA needed to review the requirements for approval of this drug product. The review of these approval requirements has the effect of permitting Nycomed to retain their eligibility for 180 day exclusivity. See memo in DARRTS dated 4/23/2009 which addressed the firms concern communicated in their 3/17/2009 letter to OGD.

Final recommendation-ANDA will be eligible for Full Approval on 2/25/2010 and should be granted 180 day exclusivity.

2. Project Manager, Esther Chuh Team 2 Review Support Branch	Date 1/25/2010 Initials EC	Date _____ Initials _____

Original Rec'd date 10/17/2006
Date Acceptable for Filing 10/17/2006
Patent Certification (type) III, IV

Date Patent/Exclus.expires 2/24/2011
Citizens' Petition/Legal Case Yes ☒ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/1/2009
Date of Office Bio Review Clnical Bio Acceptable on 1/26/2010
Date of Labeling Approv. Sum 2/15/2008
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer: Labeling Team Leader:
Date1/26/10 Date1/26/10
Name/InitialsBeverly Weitzman Name/Initials John Grace

Comments:
From: Grace, John F
Sent: Tuesday, January 26, 2010 9:27 AM
To: Weitzman, Beverly
Cc: Chuh, Esther
Subject: RE: Labeling Sign-Off: ANDA 78-548/ Nycomed/Imiquimod Cream, 5%

concur.

From: Weitzman, Beverly
Sent: Monday, January 25, 2010 8:04 PM
To: Grace, John F
Cc: Chuh, Esther
Subject: RE: Labeling Sign-Off: ANDA 78-548/ Nycomed/Imiquimod Cream, 5%

The labeling review done by Beverly Weitzman 2/14/08 and signed off by John Grace 2/15/08 remains acceptable. There are no new changes to the RLD labeling at this time. No changes noted

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 17Feb10
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date2/2/10
Chemistry Div. I InitialsPS

Comments:CMC OK.

6. Frank Holcombe **First Generics Only** Date2/18/2010
Assoc. Dir. For Chemistry InitialsRMP
Comments: (First generic drug review)
CMC is OK.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Aldara Cream, 5%
Graceway Pharmaceuticals, LLC NDA 20-723

8. Peter Rickman Date 2/19/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence study with clinical endpoints - double-blind, randomized, placebo-controlled,multi-center, parallel group study in the treatment of actinic keratoses (AK) - found acceptable 1/26/10. Statistical review also found acceptable 1/30/09.

Consult from OND dated 2/18/09 determined that the oleic acid content of the Nycomed product (b) (4) does not represent a safety issue (highest approved concentration according to IIG is 7.4%).

Final-printed labeling (FPL) found acceptable for approval 2/15/08, as endorsed 1/26/10.

CMC found acceptable for approval (Chemistry Review #3).

OR

8. Robert L. West Date 2/17/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☒ No☐
Press Release Acceptable ☐
Comments: Acceptable EES dated 4/1/09 (Verified 2/19/10). No "OAI" Alerts noted.

The agency responded on January 26, 2010 to the first Citizen Petition (P-0364) submitted by Graceway. The due date for the agency's response to the second petition submitted by Graceway (P-0423) is February 24, 2010.

Nycomed submitted a paragraph III certification to the '338 patent due to expire on February 25, 2010 (with pediatric exclusivity extension). Nycomed also submitted a paragraph IV certification to the '944 patent, but was not sued within the 45-day period. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for final approval upon expiration of the '338 patent on February 25, 2010. (provided that the agency's response to the P-0423 citizen has been issued).

9. Gary Buehler Date 2/19/10
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date_____

Review Support Branch Initials _____
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8:50 AM Time notified of approval by phone
9 AM Time approval letter faxed

FDA Notification:
2/25/2010 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/25/2010 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78548	ORIG-1	NYCOMED US INC	IMIQUIMOD

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

/s/

EUNJUNG E CHUH
02/25/2010