CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078223

Name: Clobetasol Propionate Lotion 0.05%

Sponsor: Mid Atlantic LLC

Approval Date: December 4, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

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APPLICATION NUMBER:

ANDA 078223

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-223

Actavis Mid Atlantic LLC
Attention: Janak Jadeja, R.Ph.
Director, Regulatory Affairs
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 24, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Clobetasol Propionate Lotion, 0.05%.

Reference is also made to the tentative approval letter issued by this office on May 29, 2008, and to your amendments dated May 26, 2006, and August 25, October 10, November 18, and November 25, 2008.

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 Clobetasol Propionate Lotion, 0.05%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Clobex Topical Lotion, 0.05%, of Galderma Laboratories LP. (Galderma).

The RLD upon which you have based your ANDA, Galderma's Clobex Topical Lotion, 0.05%, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 6,106,848 (the '848 patent) is scheduled to expire on September 22, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '848 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Clobetasol Propionate Lotion, 0.05%, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Actavis Mid Atlantic LLC (Actavis) for infringement of the listed '848 patent. You have notified the agency that Actavis complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '848 patent was brought against Actavis within the statutory 45-day period in the United States District Court for the Northern District of Texas, Fort Worth Division [Galderma Laboratories, L.P. and Galderma S.A. v. Actavis Mid Atlantic, L.L.C., Civil Action No. 4-06CV-471-Y]. Although this litigation remains ongoing, the 30-month period identified in section

505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, has expired.

With respect to 180-day generic drug exclusivity, we note that Actavis was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '848 patent for this drug product. Therefore, with this approval, Actavis is eligible for 180 days of generic drug exclusivity for Clobetasol Propionate Lotion, 0.05%. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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/oc/datacouncil/spl.html, 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 78-223".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
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/

Robert L. West
12/4/2008 09:20:35 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-223

Actavis Mid Atlantic LLC
Attention: Janak Jadeja, R.Ph.
Director, Regulatory Affairs
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 24, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Clobetasol Propionate Lotion, 0.05%.

Reference is made to your amendments dated May 26, 2006, June 15, 2007, and January 2, and April 8, 2008. We also acknowledge receipt of your correspondence dated May 22, and July 11, 2006, addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Clobex Topical Lotion, 0.05%, of Galderma Laboratories LP, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 6,106,848 (the '848 patent), is scheduled to expire on September 22, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '848 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Clobetasol Propionate Lotion, 0.05%, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Actavis Mid Atlantic LLC (Actavis) for

infringement of the listed '848 patent. This action must have been brought against Actavis prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Actavis complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '848 patent was brought against Actavis within the statutory 45-day period in the United States District Court for the Northern District of Texas Fort Worth Division [GALDERMA LABORATORIES, L.P. and GALDERMA S.A. v. ACTAVIS MID ATLANTIC, L.L.C., Civil Action No. 4-06CV-471-Y].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii)[1]

   b. the date the court decides[2] that the '848 patent is invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act)

   or

   c. the '848 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made.

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[1] Because information on the '848 patent was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Rosalyn Adigun, Project Manager, at (240) 276-8518.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
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/

Robert L. West
5/29/2008 12:05:54 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

LABELING

Clobetasol Propionate Lotion, 0.05%

℞ Only

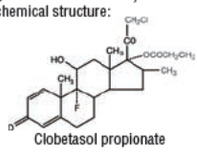
For dermatologic use only

Not for ophthalmic, oral or intravaginal use

DESCRIPTION

Clobetasol Propionate Lotion, 0.05% contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Clobetasol propionate is 21-chloro-9-fluoro-11ß,17-dihydroxy-16ß-methylpregna-1,4-diene-3, 20-dione 17-propionate, with the molecular formula $C_{25}H_{32}ClFO_5$, a molecular weight of 466.97 (CAS Registry Number 25122-46-7).

The following is the chemical structure:



Clobetasol propionate

Clobetasol propionate is a white to practically-white crystalline powder insoluble in water.

Each gram of Clobetasol Propionate Lotion, 0.05% contains 0.5 mg of clobetasol propionate, in a vehicle base composed of carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, clobetasol propionate lotion, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and occlusion. For example, occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin may increase percutaneous absorption.

There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Due to the fact that circulating levels are usually below the level of detection, the use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary. They are metabolized, primarily in the liver, and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Clobetasol propionate lotion, 0.05% is in the super-high range of potency as compared with other topical corticosteroids in vasoconstrictor studies.

In studies evaluating the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression, clobetasol propionate lotion, 0.05% demonstrated rates of suppression that were numerically higher than those of a clobetasol propionate 0.05% cream, (See **PRECAUTIONS**).

CLINICAL STUDIES

The efficacy of clobetasol propionate lotion, 0.05% in psoriasis and atopic dermatitis has been demonstrated in two adequate and well-controlled clinical trials. The first study was conducted in patients with moderate to severe plaque psoriasis. Patients were treated twice daily for 4 weeks with either clobetasol propionate lotion, 0.05% or vehicle lotion. Study results demonstrated that the efficacy of clobetasol propionate lotion, 0.05% in treating moderate to severe plaque psoriasis was superior to that of vehicle.

At the end of treatment (4 weeks), 30 of 82 patients (36.6%) treated with clobetasol propionate lotion, 0.05% compared with 0 of 29 (0%) treated with vehicle achieved success. Success was defined as a score of none or very mild (no or very slight clinical signs or symptoms of erythema, plaque elevation, or scaling) on the Global Severity scale of psoriasis.

The second study was conducted in patients with moderate to severe atopic dermatitis. Patients were treated twice daily for 2 weeks with either clobetasol propionate lotion, 0.05% or vehicle lotion. Study results demonstrated that the efficacy of clobetasol propionate lotion, 0.05% in treating moderate to severe atopic dermatitis was superior to that of vehicle.

At the end of treatment (2 weeks), 41 of 96 of patients (42.7%) treated with clobetasol propionate lotion, 0.05% compared with 4 of 33 (12.1%) treated with vehicle achieved success. Success was defined as a score of none or very mild (no or very slight clinical signs or symptoms of erythema, induration/papulation, oozing/crusting, or pruritus) on the Global Severity scale of atopic dermatitis.

INDICATIONS AND USAGE

Clobetasol Propionate Lotion, 0.05% is a super-high potent corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older (see **PRECAUTIONS**). Treatment should be limited to 2 consecutive weeks. The total dosage should not exceed 50 g (50 mL or 1.75 fl. oz.) per week.

For the treatment of moderate to severe plaque psoriasis, localized lesions (less than 10% body surface area) that have not sufficiently improved after the initial 2-week treatment with clobetasol propionate lotion, 0.05% may be treated for up to 2 additional weeks. Any additional benefits of extending treatment should be weighed against the risk of HPA axis suppression before prescribing for more than 2 weeks.

Patients should be instructed to use clobetasol propionate lotion, 0.05% for the minimum amount of time necessary to achieve the desired results (see **PRECAUTIONS**).

Use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression (see **PRECAUTIONS: Pediatric Use**).

CONTRAINDICATIONS

Clobetasol Propionate Lotion, 0.05% is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at the lowest doses tested.

Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which increase systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression (see laboratory tests below). If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

The effect of clobetasol propionate lotion, 0.05% on HPA axis function was compared to clobetasol propionate cream 0.05% in adults in two studies, one for psoriasis and one for atopic dermatitis. In total, 8 of 10 evaluable patients with moderate to severe plaque psoriasis experienced adrenal suppression following 4 weeks of clobetasol propionate lotion, 0.05% therapy (treatment beyond 4 consecutive weeks is not recommended in moderate to severe plaque psoriasis). In follow-up testing, 1 of 2 patients remained suppressed after 8 days. In this comparative study, for clobetasol propionate cream, 0.05% there were 3 of 10 evaluable patients with HPA axis suppression. Furthermore, 5 of 9 evaluable patients with moderate to severe atopic dermatitis experienced adrenal suppression following 2 weeks of clobetasol propionate lotion, 0.05% therapy (treatment beyond 2 consecutive weeks is not recommended in moderate to severe atopic dermatitis). Of the 3 patients that had follow-up testing, one patient failed to recover adrenal function 7 days post-treatment. For patients treated with clobetasol propionate cream, 0.05%, 4 of 9 evaluable patients experienced adrenal suppression following 2 weeks of treatment. Of the 2 patients that had follow-up testing, both recovered adrenal function 7 days post-treatment. The proportion of subjects suppressed may be underestimated because the adrenal glands were stimulated weekly with cosyntropin in these studies.

The potential increase in systemic exposure does not correlate with any proven benefit, but may lead to an increased potential for hypothalamic-pituitary-adrenal (HPA) axis suppression. Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression. Patients should be instructed to use clobetasol propionate lotion, 0.05% for the minimum amount of time necessary to achieve the desired results (See **INDICATIONS AND USAGE**).

If irritation develops, clobetasol propionate lotion, 0.05% should be discontinued and appropriate alternative therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as with most topical products not containing corticosteroids.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of clobetasol propionate lotion, 0.05% should be discontinued until the infection has been adequately controlled.

Clobetasol propionate lotion, 0.05% should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for Patients

Patients using topical corticosteroids should receive the following information and instructions:

PATIENT INFORMATION
Clobetasol Propionate Lotion, 0.05%

For External Use Only

Not for Ophthalmic (Eye) Use

Read the Patient Information that comes with Clobetasol Propionate Lotion 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 doctor about your medical condition or your treatment.

What is Clobetasol Propionate Lotion?

Clobetasol Propionate Lotion is a medicine called a topical (skin use only) corticosteroid. It is used for a short time to reduce the inflammation and itching of:

- Moderate to severe skin conditions (atopic dermatitis and other skin problems)
- Moderate to severe plaque psoriasis.

Clobetasol Propionate Lotion is a super-high potent (very strong) topical corticosteroid. It is very important that you use Clobetasol Propionate Lotion only as directed, in order to avoid serious side effects.

Who should not use Clobetasol Propionate Lotion?

Do not use Clobetasol Propionate Lotion if you are allergic to any of its ingredients, or to any other corticosteroid. The active ingredient is clobetasol propionate. See the end of this leaflet for the complete list of other ingredients in Clobetasol Propionate Lotion. Ask your doctor or pharmacist if you need a list of other corticosteroids.

Clobetasol Propionate Lotion is not recommended for use on anyone younger than 18 years of age. Clobetasol Propionate Lotion has not been studied in children under 12 years old. Children have smaller body sizes and have a higher chance of side effects.

What should I tell my doctor before using Clobetasol Propionate Lotion?

Tell your doctor:

- if you are pregnant, think you are pregnant, or plan to be pregnant. Talk with your doctor before using Clobetasol Propionate Lotion or if you are already using Clobetasol Propionate Lotion, as it is not known if Clobetasol Propionate Lotion can harm your unborn child.
- if you are breastfeeding. It is not known if Clobetasol Propionate Lotion passes into your milk.
- if you think you have a skin infection. You may need another medicine to treat the skin infection before you use Clobetasol Propionate Lotion.

Tell your doctor about all the other medicines and skin products you use, including prescription and non-prescription medicines, cosmetics, vitamins, and herbal supplements. Some medicines can cause serious side effects if used while you are using Clobetasol Propionate Lotion.

How should I use Clobetasol Propionate Lotion?

- Use Clobetasol Propionate Lotion exactly as directed by your doctor. Clobetasol Propionate Lotion is for skin use only.
- Apply Clobetasol Propionate Lotion twice a day, once in the morning and once at night, or as directed by your doctor. Use only enough to cover the affected areas. **Do not apply Clobetasol Propionate Lotion to your face, neck, groin or armpits. Do not get Clobetasol Propionate Lotion on your lips or in or near your eyes.**
- Make sure your skin is clean and dry before applying Clobetasol Propionate Lotion.
- Turn the bottle of Clobetasol Propionate Lotion upside down. Pour a small amount, less than 1 teaspoonful of Clobetasol Propionate Lotion onto your fingertips, or directly on your affected skin area. Gently, rub the Clobetasol Propionate Lotion into your affected skin area, until the lotion disappears.
- Wash your hands after using Clobetasol Propionate Lotion.
- If you forget to apply Clobetasol Propionate Lotion at the scheduled time, use it as soon as you remember. Then go back to your regular schedule. If it is about time for your next dose, apply just that 1 dose, and continue with your normal application schedule. Do not try to make up for the missed dose. If you miss several doses, tell your doctor.
- Throw away unused Clobetasol Propionate Lotion.

- This medication is to be used as directed by the physician and should not be used longer than the prescribed time period.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.
- Patients should wash their hands after applying the medication.
- Patients should report any signs of local or systemic adverse reactions to the physician.
- Patients should inform their physicians that they are using clobetasol propionate lotion, 0.05% if surgery is contemplated.
- This medication is for external use only. It should not be used on the face, underarms or groin area, and avoid contact with the eyes and lips.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Patients should be informed to not use more than 50 g (50 mL or 1.75 fl. oz.) per week of clobetasol propionate lotion, 0.05%.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

– Cosyntropin stimulation test
– AM plasma cortisol test
– Urinary free cortisol test

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Studies in the rat following subcutaneous administration at dosage levels up to 50 µg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of clobetasol propionate lotion, 0.05%. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 µg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of clobetasol propionate lotion, 0.05%. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

A teratogenicity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of clobetasol propionate lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobetasol propionate lotion, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when clobetasol propionate lotion, 0.05% is administered to a nursing woman.

Pediatric Use

Use of Clobetasol Propionate Lotion, 0.05% in pediatric patients is not recommended due to the potential for HPA axis suppression (see **PRECAUTIONS: General**).

The HPA axis suppression potential of clobetasol propionate lotion, 0.05% has been studied in adolescents (12 to 17 years of age) with moderate to severe atopic dermatitis covering a minimum of 20% of the total body surface area. In total 14 patients were evaluated for HPA axis function. Patients were treated twice daily for 2 weeks with clobetasol propionate lotion, 0.05%. After 2 weeks of treatment, 9 out of 14 of the patients experienced adrenal suppression. One out of 4 patients treated with clobetasol propionate lotion, 0.05% who were retested remained suppressed two weeks post-treatment. In comparison, 2 of 10 of the patients treated with clobetasol propionate cream, 0.05% demonstrated HPA axis suppression. One patient who was retested recovered.

None of the patients who developed HPA axis suppression had concomitant clinical signs of adrenal suppression and none of them was discontinued from the study for reasons related to the safety or tolerability of clobetasol propionate lotion, 0.05%. However, patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use

Clinical studies of clobetasol propionate lotion, 0.05% did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In controlled clinical trials with clobetasol propionate lotion, 0.05%, the following adverse reactions have been reported: burning/stinging, skin dryness, irritation, erythema, folliculitis, pruritus, skin atrophy, and telangiectasia.

The pooled incidence of local adverse reactions in trials for psoriasis and atopic dermatitis with clobetasol propionate lotion, 0.05% at 1.0% or greater was:

Adverse Reaction	Incidence
Skin Atrophy	4.2%
Telangiectasia	3.2%
Discomfort Skin	1.3%
Skin Dry	1.0%

Other local adverse events occurred at rates less than 1.0%. Similar rates of local adverse reactions were reported in the comparator (clobetasol propionate cream, 0.05%). Most local adverse events were rated as mild to moderate and they are not affected by age, race or gender.

The following additional local adverse reactions have been reported with topical corticosteroids. They may occur more frequently with the use of occlusive dressings and higher potency corticosteroids including clobetasol propionate. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

OVERDOSAGE

Topically applied clobetasol propionate lotion, 0.05% can be absorbed in sufficient amount to produce systemic effects (See **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Clobetasol Propionate Lotion, 0.05% should be applied to the affected skin areas twice daily and rubbed in gently and completely. (See **INDICATIONS AND USAGE.**)

Clobetasol Propionate Lotion, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to:

– 2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses,
– and up to 2 additional weeks in very localized lesions of moderate to severe plaque psoriasis (no more than 10% body surface area) that have not sufficiently improved after the initial 2 weeks of treatment with clobetasol propionate lotion, 0.05%.

The total dosage should not exceed 50 g (50 mL or 1.75 fl. oz.) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Use in patients younger than 18 years is not recommended because of numerically high rates of HPA axis suppression (See **PRECAUTIONS: Pediatric Use**).

Unless directed by physician, Clobetasol Propionate Lotion, 0.05% should not be used with occlusive dressings.

HOW SUPPLIED

Clobetasol Propionate Lotion, 0.05% is supplied in the following sizes:

1 fl. oz. (30 mL) high density polyethylene bottles.
2 fl. oz. (59 mL) high density polyethylene bottles.
4 fl. oz. (118 mL) high density polyethylene bottles.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Manufactured by: Actavis Mid Atlantic LLC
1877 Kawai Road, Lincolnton, NC 28092 USA

FORM NO. 0404 Rev. 8/08
VC3157

What should I avoid while using Clobetasol Propionate Lotion?

Do not do the following while using Clobetasol Propionate Lotion:

- **Do not get Clobetasol Propionate Lotion on your face, lips, or in or near your eyes** because this might cause irritation. If you do, use a lot of water to rinse the Clobetasol Propionate Lotion off your face, lips, or out of your eyes. If your eyes keep stinging after rinsing them well with water, call your doctor right away.
- **Do not apply Clobetasol Propionate Lotion to your groin or armpits.**
- **Do not bandage or cover your treated areas unless your doctor tells you to do so.**
- **Do not wear tight fitting clothes over your treated skin areas.**
- **Do not use Clobetasol Propionate Lotion any longer than 2 weeks** (14 days) for moderate to severe conditions (atopic dermatitis and other skin problems).
- **Do not use Clobetasol Propionate Lotion any longer than an extra 2 weeks** (4 weeks total) for psoriasis on a small area of your body (less than 10 percent of your body surface area) that is not much better after the first 2 weeks of treatment.
- **Do not use more than 50 grams (50 mL or 1.75 fluid ounces) of Clobetasol Propionate Lotion a week.** Clobetasol Propionate Lotion comes in 3 different size bottles, a 1-ounce, 2-ounce, and 4-ounce bottle.

What are the possible side effects of Clobetasol Propionate Lotion?

Clobetasol Propionate Lotion can pass through your skin. Too much Clobetasol Propionate Lotion passing through your skin can shut down your adrenal glands. This usually happens if you use too much Clobetasol Propionate Lotion, or you use it for too long. If this happens, your adrenal glands may not start working immediately once you stop using Clobetasol Propionate Lotion. **Shutting down of the adrenal glands can cause nausea, vomiting, fever, low blood pressure, heart attack, and even death because your body cannot respond to any stress or illness.**

Your doctor may do special blood and urine tests to check your adrenal gland function while you are using Clobetasol Propionate Lotion.

Other possible side effects with Clobetasol Propionate Lotion include mild burning, stinging, itching, redness, irritation, and dry skin. Also, thinning of the skin, widening of small blood vessels in the skin, and skin discomfort at the site of application may happen. Sometimes your condition will get worse with use of Clobetasol Propionate Lotion.

If you are ill or injured, or going to have surgery, tell your doctor that you are using Clobetasol Propionate Lotion.

Tell your doctor if you:

- **are going to have surgery.**
- **get sick or don't feel right. Call your doctor right away.**
- have irritation of the treated skin area that does not go away.
- have any unusual effects that you do not understand.
- have affected areas that do not seem to be getting better after 2 weeks of using Clobetasol Propionate Lotion.

These are not all the possible side effects of Clobetasol Propionate Lotion. For more information, ask your doctor or pharmacist.

General information about the safe and effective use of Clobetasol Propionate Lotion.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Clobetasol Propionate Lotion for a condition for which it was not prescribed. Do not give Clobetasol Propionate Lotion to other people, even if they have the same symptoms you have. It may harm them. **Keep Clobetasol Propionate Lotion and all medicines out of reach of children.**

This leaflet summarizes the most important information about Clobetasol Propionate Lotion. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Clobetasol Propionate Lotion that is written for health professionals.

What are the ingredients of Clobetasol Propionate Lotion?

Active Ingredient: clobetasol propionate

Inactive Ingredients: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

Manufactured by: Actavis Mid Atlantic LLC
1877 Kawai Road, Lincolnton, NC 28092 USA

FORM NO. 0404 Rev. 8/08
VC3157

actavis

NDC 0472-**0404**-91

℞ Only

Clobetasol

Propionate Lotion

0.05%

Topical Lotion

For External Use Only
Not For Eye Use

1 fl oz (30 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.
EACH GRAM CONTAINS: Active: clobetasol propionate 0.5 mg.
Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.
Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].
See label for lot number and expiration date.
040412O6C1 VC2935
Manufactured by: Actavis Mid Atlantic LLC
1877 Kawai Road, Lincolnton, NC 28092 USA

actavis

NDC 0472-**0404**-92

℞ Only

Clobetasol

Propionate Lotion

0.05%

Topical Lotion

For External Use Only

Not For Eye Use

2 fl oz (59 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.
EACH GRAM CONTAINS: Active: clobetasol propionate 0.5 mg.
Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.
Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].
See label for lot number and expiration date.

actavis 04041206C1 VC2936

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1877 Kawai Road, Lincolnton, NC 28092 USA

actavis

NDC 0472-**0404**-94

℞ Only

Clobetasol
Propionate Lotion
0.05%
Topical Lotion

For External Use Only
Not For Eye Use

4 fl oz (118 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.

EACH GRAM CONTAINS: Active: clobetasol propionate 0.5 mg. Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

See label for lot number and expiration date.

04041206C1 VC2937

actavis

Manufactured by: Actavis Mid Atlantic LLC
1877 Kawai Road, Lincolnton, NC 28092 USA

actavis

NDC 0472-**0404**-91

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

1 fl oz (30 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.

EACH GRAM CONTAINS:
Active: clobetasol propionate 0.5 mg.
Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

See carton for lot number and expiration date.

04041206C1 VC2934

Clobetasol
Propionate Lotion
0.05%

actavis

NDC 0472-0404-91

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

1 fl oz (30 mL)

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Manufactured by:
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1877 Kawai Road
Lincolnton, NC 28092 USA

N 3 04720 40491 0

actavis

NDC 0472-**0404**-92

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

2 fl oz (59 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.

EACH GRAM CONTAINS:
Active: clobetasol propionate 0.5 mg.
Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].
See carton for lot number and expiration date.

04041206C1 VC106864

actavis

NDC 0472-**0404**-92

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

2 fl oz (59 mL)

actavis
Manufactured by:
Actavis Mid Atlantic LLC
1877 Kawai Road
Lincolnton, NC 28092 USA

N 3 04720 40492 7

actavis

NDC 0472-**0404**-94

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

4 fl oz (118 mL)

USUAL DOSAGE: Apply twice daily, once in the morning and once at night.
Use only enough to cover the affected areas. Do not apply clobetasol propionate topical lotion, 0.05% to the face, underarms, or groin and avoid contact with eyes and lips.
See package insert for complete prescribing information.

EACH GRAM CONTAINS:
Active: clobetasol propionate 0.5 mg.
Inactive: carbomer 940, hypromellose, mineral oil, polyoxyethylene glycol 300 isostearate, polysorbate 80, propylene glycol, purified water, and sodium hydroxide.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].
See carton for lot number and expiration date.

04041206C1
VC106865

Clobetasol
Propionate Lotion
0.05%

actavis

NDC 0472-0404-94

Clobetasol
Propionate Lotion
0.05%

Topical Lotion

For External Use Only
Not For Eye Use

℞ Only

4 fl oz (118 mL)

actavis

Manufactured by:
Actavis Mid Atlantic LLC
1877 Kawai Road
Lincolnton, NC 28092 USA

N 3 04720 40494 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

LABELING REVIEWS

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

ANDA Number: 78-223

Date of Submission: **March 24, 2006**

Applicant's Name: Alpharma USPD Inc.

Established Name: Clobetasol Propionate Lotion, 0.05%.

Labeling Deficiencies:

1. **GENERAL COMMENT: [ALL LABELING] -** Revise your storage temperature on your labels and labeling to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]".
2. **CONTAINER** (30mL, 59 mL) - See General Comment.
3. **CARTON** (30 mL, 59 mL) – See General Comment.
4. **PROFESSIONAL INSERT -** See general Comment.
5. **PATIENT INFORMATION:** Satisfactory in Draft.

   Please ensure that the instructions for use are provided as a separate labeling piece within the carton or that they may be separated from the physician labeling as a distinct piece.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of 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?

1. CONTAINER -

2. **CONTAINER -**

3. **CARTON -**

4. **CARTON -**

5. **PACKAGE INSERT** -

6. PATIEN INFORMATION -

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: **Clobex Lotion**
- NDA Number: 21-535
- NDA Drug Name: Clobetasol Propionate Lotion, 0.05%.
- NDA Firm: Galderma Laboratories
- Date of Approval of NDA Insert and supplement **21-535: Approved July 24, 2003**
- 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 comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup	Expiration	Use Code	Description		Labeling Impact
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling for the reference listed drug, Clobex Lotion, 0.05% [NDA 21-535: Approved July 24, 2003] by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup	Expiration	Use Code	Description		Labeling Impact
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

3. INACTIVE INGREDIENTS

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

Ingredients	function
Clobetasol Propionate USP	Active ingredient
Carbomer 940 NF	(b) (4)
Propylene Glycol USP	

Hypromellose USP	(b) (4)	(b) (4)
Mineral Oil USP		
Polyoxyethylene Glycol 300 isostearate		
Polysorbate 80 NF		
Sodium Hydroxide NF		
Purified water USP		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers. Store at controlled room temperature. Do not refrigerate.
- RLD: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing
- ANDA: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing

5. PACKAGE CONFIGURATION

- RLD: Packaged in 1 oz, 2 oz, and 4 oz high density polyethylene bottles
- ANDA:

Package size	HDPE bottle	Polypropylene Cap
1 ounce	1 oz (b) (4) white, bottom round, HDPE	(b) (4) white, polypropylene, press-top
2 ounce	2 oz (b) (4) white, cylinder, HDPE	(b) (4) white, polypropylene, press-top

6. CONTAINER/CLOSURE:

Component	Manufacturer	DMF #
Bottle: 1 oz white, bottom round, HDPE and 2 oz white, cylinder, HDPE (b) (4)	(b) (4)	

7. FNISHED DOSAGE FORM

- RLD: Lotion
- ANDA: White emulsion

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Alpharma USPD Inc. (a subsidiary of Actavis Group)
1877 Kawai Road
Lincolnton, NC 28092
CFN# 1053439

Date of Review: **Date of Submission: March 24, 2006**

Primary Reviewer: B. 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
11/29/2006 12:00:36 PM
MEDICAL OFFICER

John Grace
11/29/2006 01:15:06 PM
MEDICAL OFFICER

APPROVAL SUMMARY #1

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

ANDA Number: 78-223 Date of Submission: June 15, 2007 and **January 2, 2008**

Applicant's Name: Alpharma USPD Inc.

Established Name: Clobetasol Propionate Lotion, 0.05%.

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

1. CONTAINER (1 oz) - Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\contain.pdf

2. **CONTAINER (2 oz) -** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
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3. **CONTAINER (4 oz) -** Satisfactory in Final Print as of **January 2, 2008** electronic submission
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\contain.pdf

4. **CARTON (1 oz)-** Satisfactory in Final Print as of **January 2 , 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

5. **CARTON (2 oz)-** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

6. **CARTON (4 oz)-** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

7. **PACKAGE INSERT** - Satisfactory in Final Print as of **January 2 , 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\pi.pdf

8. PATIEN INFORMATION - Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\pi.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: **Clobex Lotion**
- NDA Number: 21-535
- NDA Drug Name: Clobetasol Propionate Lotion, 0.05%.
- NDA Firm: Galderma Laboratories
- Date of Approval of NDA Insert and supplement **21-535: Approved July 24, 2003**
- 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 comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup	Expiration	Use Code	Description		Labeling Impact
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

NOTE TO CHEMIST: Please note that the firm added a new package size, 4 oz bottle in addition to the 1 oz and 2 oz bottles.

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling for the reference listed drug, Clobex Lotion, 0.05% [NDA 21-535: Approved July 24, 2003] by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup	Expiration	Use Code	Description		Labeling Impact
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

3. INACTIVE INGREDIENTS

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

Ingredients	function
Clobetasol Propionate USP	Active ingredient
Carbomer 940 NF	(b) (4)
Propylene Glycol USP	
Hypromellose USP (b) (4)	
Mineral Oil USP	
Polyoxyethylene Glycol 300 isostearate	
Polysorbate 80 NF	
Sodium Hydroxide NF	
Purified water USP	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers. Store at controlled room temperature. Do not refrigerate.
- RLD: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing
- ANDA: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing

5. PACKAGE CONFIGURATION

- RLD: Packaged in 1 oz, 2 oz, and 4 oz high density polyethylene bottles
- ANDA: Package in 1 oz, 2 oz and **4 oz.** The firm submitted a labeling amendment June 15, 2007 to provide for a new package size, 4 oz bottle.

Package size	HDPE bottle	Polypropylene Cap
1 ounce	1 oz (b) (4) white, bottom round, HDPE	(b) (4) white, polypropylene, press-top
2 ounce	2 oz (b) (4) white, cylinder, HDPE	(b) (4) white, polypropylene, press-top

6. CONTAINER/CLOSURE:

Component	Manufacturer	DMF #
Bottle: 1 oz white, bottom round, HDPE and 2 oz white, cylinder, HDPE (b) (4)	(b) (4)	

(b) (4)	(b) (4)

7. FNISHED DOSAGE FORM

- RLD: Lotion
- ANDA: White emulsion

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Alpharma USPD Inc. (a subsidiary of Actavis Group)
1877 Kawai Road
Lincolnton, NC 28092
CFN# 1053439

Date of Submission: June 15, 2007 and January 2, 2008

Primary Reviewer: B. 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
1/22/2008 09:56:17 AM
LABELING REVIEWER

John Grace
1/22/2008 02:29:22 PM
LABELING REVIEWER

APPROVAL SUMMARY #2

Supercedes Approval Summary #1 from June 15, 2007 and January 2, 2008 submissions

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

ANDA Number: 78-223

Date of Submission: August 25, 2008 (Revised Insert)

Applicant's Name: Alpharma USPD Inc.

Established Name: Clobetasol Propionate Lotion, 0.05%.

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

1. CONTAINER (1 oz) - Satisfactory in Final Print as of **January 2, 2008** electronic submission.
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2. **CONTAINER (2 oz) -** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\contain.pdf

3. **CONTAINER (4 oz) -** Satisfactory in Final Print as of **January 2, 2008** electronic submission
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\contain.pdf

4. **CARTON (1 oz)-** Satisfactory in Final Print as of **January 2 , 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

5. **CARTON (2 oz)-** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

6. **CARTON (4 oz)-** Satisfactory in Final Print as of **January 2, 2008** electronic submission.
\\Cdsesub1\nonectd\N78223\N_000\2008-01-02\Amendment (Labeling)\labeling\carton.pdf

7. **PACKAGE INSERT** - Satisfactory in Final Print as of **August 25 , 2008** electronic submission.
\\Fdswa150\nonectd\N78223\N_000\2008-08-25\Amendment (Labeling)\labeling\pi-final.pdf

8. PATIEN INFORMATION - Satisfactory in Final Print as of **August 25, 2008** electronic submission.
\\Fdswa150\nonectd\N78223\N_000\2008-08-25\Amendment (Labeling)\labeling\pi-final.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: **Clobex Lotion**
- NDA Number: 21-535
- NDA Drug Name: Clobetasol Propionate Lotion, 0.05%.
- NDA Firm: Galderma Laboratories
- Date of Approval of NDA Insert and supplement **21-535: Approved July 24, 2003**
- 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 comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup		Use	Description		Labeling Impact

	Expiration	Code			
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

NOTE TO CHEMIST: Please note that the firm added a new package size, 4 oz bottle in addition to the 1 oz and 2 oz bottles.

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling for the reference listed drug, Clobex Lotion, 0.05% [NDA 21-535: Approved July 24, 2003] by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 21-535

No	Expiration	Use Code	Use	File
6106848	September 22, 2017			IV

Exclusivity Data - NDA 21-535

Code/sup	Expiration	Use Code	Description		Labeling Impact
	July 24, 2006	NDF	New Dosage Form		EXPIRED - NONE

3. INACTIVE INGREDIENTS

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

Ingredients	function
Clobetasol Propionate USP	Active ingredient
Carbomer 940 NF	(b) (4)
Propylene Glycol USP	
Hypromellose USP (b) (4)	
Mineral Oil USP	
Polyoxyethylene Glycol 300 isostearate	
Polysorbate 80 NF	
Sodium Hydroxide NF	
Purified water USP	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers. Store at controlled room temperature. Do not refrigerate.
- RLD: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing
- ANDA: Store at controlled room temperature Store at 68 - 77°F (20 - 25°C). Protect from freezing

5. PACKAGE CONFIGURATION

- RLD: Packaged in 1 oz, 2 oz, and 4 oz high density polyethylene bottles
- ANDA: Package in 1 oz, 2 oz and **4 oz.** The firm submitted a labeling amendment June 15, 2007 to provide for a new package size, 4 oz bottle.

Package size	HDPE bottle	Polypropylene Cap
1 ounce	1 oz (b) (4) white, bottom round, HDPE	(b) (4) white, polypropylene, press-top
2 ounce	2 oz (b) (4) white, cylinder, HDPE	(b) (4) white, polypropylene, press-top

6. CONTAINER/CLOSURE:

Component	Manufacturer	DMF #
Bottle: 1 oz white, bottom round, HDPE and 2 oz white, cylinder, HDPE	(b) (4)	
(b) (4)		

7. FNISHED DOSAGE FORM

- RLD: Lotion
- ANDA: White emulsion

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Alpharma USPD Inc. (a subsidiary of Actavis Group)
1877 Kawai Road
Lincolnton, NC 28092
CFN# 1053439

Date of Submission: August 25, 2008

Primary Reviewer: B. 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
9/17/2008 03:24:37 PM
LABELING REVIEWER

John Grace
9/18/2008 01:10:39 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

CHEMISTRY REVIEWS

ANDA 78-223

Clobetasol Propionate Lotion, 0.05%

Actavis Mid Atlantic LLC

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-223

2. REVIEW #:1

3. REVIEW DATE: 27-Jun-2006

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 24, 2006
Acceptable for filing	March 27, 2006

7. NAME & ADDRESS OF APPLICANT:

Actavis Mid Altantic LLC
Attention: Janak Jadeja
200 Elmora Avenue
Elizabeth, NJ 07207
Tel: 732-465-3631

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Clobetasol Propionate Lotion, 0.05%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Clobex™ Topical Lotion, 0.05% manufactured by Galderma Labs LP
NDA 021535, NDA holder: Galderma Labs LP
Alpharma, USPD, Inc. Proposed drug product: Clobetasol Propionate Lotion, 0.05%
Active ingredient, route of administration, dosage form, and strength of the proposed drug product: are the same as that of the RLD

Patent certification:

US patent number	expiration date
6,106,848	September 22, 2017

Paragraph IV certification
Alpharma, USPD, Inc., hereby certifies that US patent # 6106848 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Alpharma,'s Clobetasol Propionate Lotion, 0.05% for which this application is submitted.

Marketing exclusivity statement
New dosage form

The listed drug Clobex™ Topical Lotion, 0.05% is entitled to a period of marketing exclusivity for a new dosage form (NDF). Alpharma plans to market Clobetasol Propionate Lotion, 0.05% once the new dosage form exclusivity has expired.

10. PHARMACOL. CATEGORY:

Clobetasol Propionate Lotion is indicated for relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses and for the treatment of moderate to severe plaque psoriasis.

11. DOSAGE FORM:

Lotion (Topical use)

12. STRENGTH/POTENCY:

0.05%

13. ROUTE OF ADMINISTRATION:

Topical use

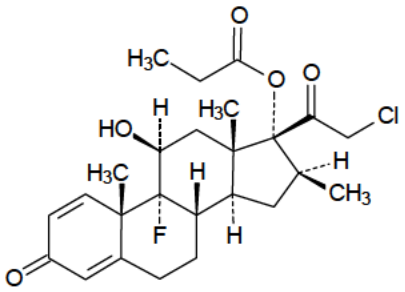
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-.$C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7.
Anti-inflammatory.



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	Inadequate	9/21/06	Reviewer: LL Huang, Ph.D.
	III			4			
	III			4			
	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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	5/17/06	
Methods Validation	Not required		
Labeling	pending		
Bioequivalence	pending		
EA	EA is 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. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-223

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 78-223 is not 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)

Drug product

The drug product is prepared using the following procedures:

(b) (4)

(b) (4)

Drug substance
Clobetasol Propionate USP drug substance is a white to cream crystalline powder, Its melting range is approximately 196°C.

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

Clobetasol Propionate Lotion is used for relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses and for the treatment of moderate to severe plaque psoriasis.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the deficiencies found in the following areas.

- The firm needs to evaluate (b) (4) .
- The firm needs to include (b) (4)
- The firm needs to include (b) (4)
- The firm needs to provide (b) (4) .

Following this page, 6 pages withheld in full (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Method validation is not required.

32. LABELING
Pending review

On page162 the firm stated that the specification for unknown related compounds is set in agreement with the IT (identification threshold) of 0.10% prescribed in ICH Q3A (R) for drug substances with a maximum daily dose of ≤2 g/day. The statement "… with a maximum daily dose of ≤2 g/day" is incorrect. The correct answer should be ≤1 g/day.

33. ESTABLISHMENT INSPECTION
Acceptable 5/17/06

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS
Pending review

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

satisfactory
Pursuant to 21 CFR 25.31 (a) Alpharma hereby requests a categorical exclusion from the requirement of an environment assessment.
The drug product covered by this application is not expected to increase the use of the active moiety.
Alpharma USPD, Inc., certifies that the firm is in compliance with all federal, state and local environmental regulations.

36. Chemistry Comments to be Provided to the Applicant

ANDA: 78-223 APPLICANT: Actavis Mid Atlantic LLC

DRUG PRODUCT: Clobetasol Propionate Lotion, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please evaluate [redacted] (b) (4)
2. Please qualify [redacted] (b) (4)
3. Please include [redacted] (b) (4)
4. DMF [redacted] (b) (4) has been reviewed and found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has notified you that they have answered their deficiencies.
5. Please include [redacted] (b) (4).
6. Please provide [redacted] (b) (4).
7. Please include [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 provide all available long-term drug product stability data.

2. USP methods are the regulatory methods for the drug substance. In the event of a dispute, the USP methods will prevail.

3. Information related to the labeling and bioequivalency is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

4. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

5. On page162 you stated that the specification for unknown related compounds is set in agreement with the IT (identification threshold) of 0.10% prescribed in ICH Q3A (R) for drug substances with a maximum daily dose of ≤2 g/day. The statement "… with a maximum daily dose of ≤2 g/day" is incorrect. The correct answer should be ≤1 g/day.

Sincerely yours,

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

cc: ANDA 78-223
ANDA DUP 78-223
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /6/26/06;9/22/06, 10/3/06

HFD-627/ James Fan, Team Leader/6/27/06 ;9/23/06

HFD-617/R. Adigun, Project Manager/9/29/06

F/T:ard/10/2/06, 10/16/06

V:\FIRMSAM\Alpharma.usp\LTRS&REV\78-223 rev1.doc

November 16, 2006

TYPE OF LETTER: NOT APPROVABLE -MINOR/

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

/s/

Liang Lii Huang
11/28/2006 02:48:33 PM
CHEMIST

Rosalyn Adigun
11/30/2006 10:54:14 AM
CSO

James Fan
12/1/2006 10:34:20 AM
CHEMIST

ANDA 78-223

Clobetasol Propionate Lotion, 0.05%

Actavis Mid Atlantic LLC

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 78-223

2. REVIEW #: 2

3. REVIEW DATE: 10-Apr-2008

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 24, 2006
Acceptable for filing	March 27, 2006
Minor amendment and Gratuitous information	June 15, 2007
Telephone amendment	April 8, 2008

7. NAME & ADDRESS OF APPLICANT:

Actavis Mid Altantic LLC
Attention: Janak Jadeja
200 Elmora Avenue
Elizabeth, NJ 07207
Tel: 732-465-3631

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Clobetasol Propionate Lotion, 0.05%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Clobex™ Topical Lotion, 0.05% manufactured by Galderma Labs LP
NDA 021535, NDA holder: Galderma Labs LP
Alpharma, USPD, Inc. Proposed drug product: Clobetasol Propionate Lotion, 0.05%
Active ingredient, route of administration, dosage form, and strength of the proposed drug product: are the same as that of the RLD

Patent certification:

US patent number	expiration date
6,106,848	September 22, 2017

Paragraph IV certification
Alpharma, USPD, Inc., hereby certifies that US patent # 6106848 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Alpharma,'s Clobetasol Propionate Lotion, 0.05% for which this application is submitted.

Marketing exclusivity statement
New dosage form

The listed drug Clobex™ Topical Lotion, 0.05% is entitled to a period of marketing exclusivity for a new dosage form (NDF). Alpharma plans to market Clobetasol Propionate Lotion, 0.05% once the new dosage form exclusivity has expired.

10. PHARMACOL. CATEGORY:

Clobetasol Propionate Lotion is indicated for relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses and for the treatment of moderate to severe plaque psoriasis.

11. DOSAGE FORM:

Lotion (Topical use)

12. STRENGTH/POTENCY:

0.05%

13. ROUTE OF ADMINISTRATION:
Topical use

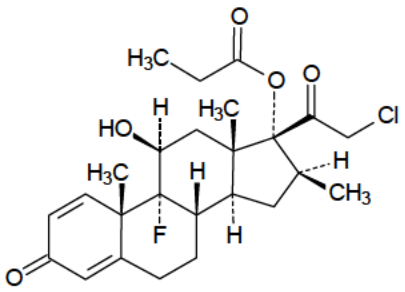
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-.$C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7.
Anti-inflammatory.



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	2/25/08	Reviewer: LL Huang, Ph.D.
	III			4			
	III			4			
	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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	5/17/06	
Methods Validation	Not required		
Labeling	Acceptable	1/22/08	B. Weitzman
Bioequivalence	Acceptable	2/14/07	B. Li
EA	EA is 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. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-223

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 78-223 is approvable.

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

N/A

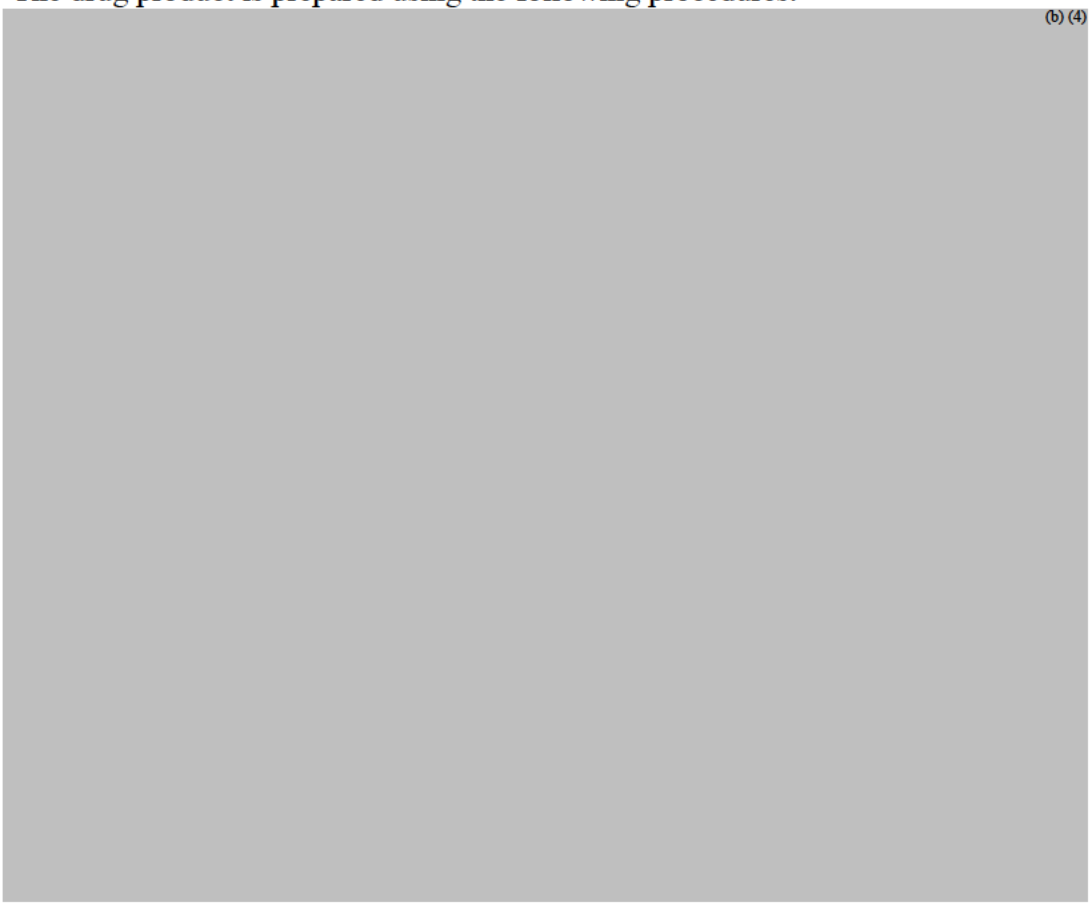
II. Summary of Chemistry Assessments

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

Drug product

The drug product is prepared using the following procedures:

(b) (4)



(b) (4)

Drug substance
Clobetasol Propionate USP drug substance is a white to cream crystalline powder, Its melting range is approximately 196°C.

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

Clobetasol Propionate Lotion is used for relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses and for the treatment of moderate to severe plaque psoriasis.

MDD = 3.57 mg/day (package insert: 50 g per week)
7.14 g/day X 0.05% = 3.57 mg/day

DS	IT = 0.10%	QT = 0.15%
DP	IT = 0.50%	QT = 1.0%

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

Following this page, 18 pages withheld in full (b)(4)

(b) (4)

30. MICROBIOLOGY

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation is not required.

32. LABELING

Acceptable 1/22/08

33. ESTABLISHMENT INSPECTION

Acceptable 5/17/06

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS

Acceptable 2/14/07

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory as per review #1

cc: ANDA 78-223
ANDA DUP 78-223
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /2/13/08;2/25/08;4/9/08

HFD-627/ James Fan, Team Leader/2/14/08;2/25/08;4/9/08

HFD-617/R. Adigun, Project Manager/2/14/08;2/25/08; 4/9/08

F/T:

V:\FIRMSAM\Alpharma.usp\LTRS&REV\78-223 rev2.doc

April 9, 2008

TYPE OF LETTER: APPROVABLE

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

/s/

Liang Lii Huang
5/29/2008 10:56:44 AM
CHEMIST

James Fan
5/29/2008 02:54:38 PM
CHEMIST

Rosalyn Adigun
5/29/2008 02:59:52 PM
CSO

ANDA 78-223

Clobetasol Propionate Lotion, 0.05%

Actavis Mid Atlantic LLC

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 78-223

2. REVIEW #: 3

3. REVIEW DATE: 14-Nov-2008

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 24, 2006
Acceptable for filing	March 27, 2006
Minor amendment and Gratuitous information	June 15, 2007
Telephone amendment	April 8, 2008
Tentative approval	May 29, 2008
Minor amendment – Final approval requested	October 10, 2008
Telephone amendment	November 18, 2008
Telephone amendment	November 25, 2008

7. NAME & ADDRESS OF APPLICANT:

Actavis Mid Atlantic LLC
Attention: Janak Jadeja
200 Elmora Avenue
Elizabeth, NJ 07207
Tel: 732-465-3631

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Clobetasol Propionate Lotion, 0.05%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Clobex™ Topical Lotion, 0.05% manufactured by Galderma Labs LP
NDA 021535, NDA holder: Galderma Labs LP
Alpharma, USPD, Inc. Proposed drug product: Clobetasol Propionate Lotion, 0.05%
Active ingredient, route of administration, dosage form, and strength of the proposed drug product: are the same as that of the RLD

Patent certification:

US patent number	expiration date
6,106,848	September 22, 2017

Paragraph IV certification
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Marketing exclusivity statement
New dosage form

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10. PHARMACOL. CATEGORY:

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11. DOSAGE FORM:

Lotion (Topical use)

12. STRENGTH/POTENCY:
0.05%

13. ROUTE OF ADMINISTRATION:
Topical use

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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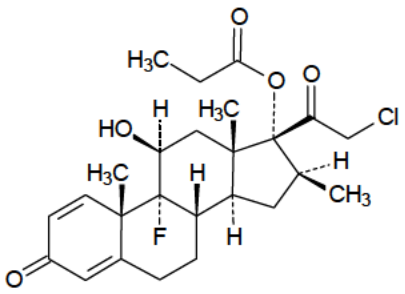
Anti-inflammatory.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	2/25/08	Reviewer: LL Huang, Ph.D.
	III			4			
	III			4			
	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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/24/08	
Methods Validation	Not required		
Labeling	Acceptable	9/18/08	B. Weitzman
Bioequivalence	Acceptable	2/14/07	B. Li
EA	EA is 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. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-223

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 78-223 is approvable.

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

N/A

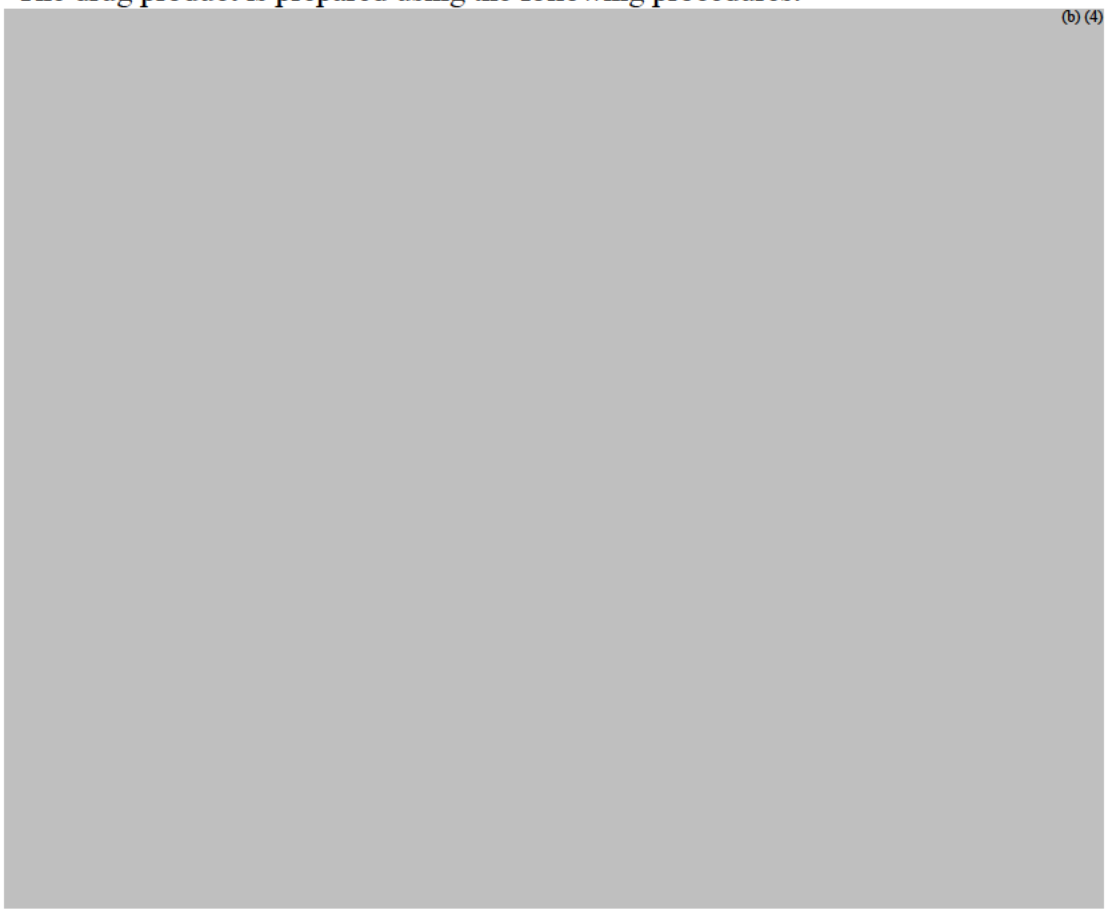
II. Summary of Chemistry Assessments

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

Drug product

The drug product is prepared using the following procedures:

(b) (4)



(b) (4)

Drug substance
Clobetasol Propionate USP drug substance is a white to cream crystalline powder, Its melting range is approximately 196°C.

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

Clobetasol Propionate Lotion is used for relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses and for the treatment of moderate to severe plaque psoriasis.

MDD = 3.57 mg/day (package insert: 50 g per week)
7.14 g/day X 0.05% = 3.57 mg/day

DS	IT = 0.10%	QT = 0.15%
DP	IT = 0.50%	QT = 1.0%

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

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(b) (4)

30. MICROBIOLOGY

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation is not required.

32. LABELING

Acceptable 9/18/08

33. ESTABLISHMENT INSPECTION

Acceptable 11/24/08

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS

Acceptable 2/14/07

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory as per review #1

cc: ANDA 78-223
ANDA DUP 78-223
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /11/14/08; 11/20/08

HFD-627/ James Fan, Team Leader/11/14/08; 11/20/08

HFD-617/R. Adigun, Project Manager/11/20/08

F/T:

V:\Chemistry Division I\Team 3\FIRMSAM\ACTAVIS MID ATL LLC\LTRS&RVS\78-223 rev3.doc

November 20, 2008

TYPE OF LETTER: APPROVABLE

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

/s/

Liang Lii Huang
12/4/2008 10:33:33 AM
CHEMIST

James Fan
12/4/2008 12:48:49 PM
CHEMIST

Rosalyn Adigun
12/4/2008 01:03:10 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-223
Drug Product Name	Clobetasol Propionate Lotion
Strength	0.05%
Applicant Name	Alpharma USPD, Inc.
Address	Attention: Janak Jadeja One New England Avenue, Piscataway, NJ 08854 732-465-3631 (phone), 732-465-3731 (fax)
Submission Date(s)	March 24, 2006
Amendment Date(s)	NA
Reviewer	Bing V. Li
First Generic	No

I. Executive Summary

The application contains the results of a Pilot Dose Duration-Response Study and a Pivotal Pharmacodynamic (PD) Bioequivalence (BE) Study comparing the test product, Clobetasol Propionate Lotion, 0.05% from Alpharma USPD, Inc. to the Reference Listed Drug (RLD), CLOBEX®, 0.05%, from Galderma Labs LP.

The Pilot Dose Duration-Response Study of CLOBEX®, 0.05%, was performed in 15 healthy volunteers. The study resulted in D1, ED50, and D2 data of 3, 6, and 12 minutes respectively. The ED50 as determined by the DBE was the same as the firm's results.

The Pivotal PD BE Study of test product Clobetasol Propionate Lotion, 0.05% and the RLD, CLOBEX®, 0.05%, was performed in 224 healthy volunteers (females). For the pivotal study analysis, 64 subjects met the D2/D1 $\geq$ 1.25 criterion. Analysis of the qualified subjects in the study resulted in a point-estimate of 104.2 and 90% confidence interval of 87.6-124.2 using Locke's method for the $AUEC_{0-24}$ data. The study is therefore acceptable.

The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	CLOBETASOL PROPIONATE LOTION, 0.05%
Reference Product	CLOBEX®, 0.05%
RLD Manufacturer	Galderma Labs LP
NDA No.	21-535
RLD Approval Date	Jul 24, 2003
Indication	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses and for the treatment of moderate to severe plaque psoriasis

B. PK/PD Information

Background

Clobetasol propionate belongs to topical corticosteroid. There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systematically administered corticosteroids. Due to the fact that circulating levels are usually below the level of detection, the use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary. They are metabolized, primarily in the liver, and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

CLOBEX® (clobetasol propionate) Lotion, 0.05% is in the super-high range of potency as compared with other topical corticosteroids in vasoconstrictor studies.

In studies evaluating the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression, CLOBEX® Lotion, 0.05% demonstrated rates of suppression that were numerically higher than those of a clobetasol propionate 0.05% cream (Temovate E® Emollient, 0.05%).

Relevant OGD or DBE History

DBE has not reviewed any clobetasol propionate lotion. However, DBE has reviewed a number of clobetasol propionate in other topical dosage forms, such as cream, gel, ointment, and topical solution.

DBE has reviewed only one protocol of clobetasol propionate lotion (P00-015, (b) (4), Submission Date: April 26, 2000). DEB recommended the firm to conduct a clinical end point bioequivalence study, a vasoconstrictor assay, and an HPA-axis suppression study.

Agency Guidance

Guidance for Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, Issued June 2, 1995 and Posted 06 March 1998.

Drug Specific Issues

Topical corticosteroids cause vasoconstriction of the skin micro-vasculature, leading to blanching of treated skin areas. The vasoconstrictor response of topical corticosteroids can be measured as a function of dose or the length of the time for exposure to the skin. A pharmacodynamic assay based on quantitation of the vasoconstrictor response has been adopted by the agency for documentation of bioequivalence of multisource topical corticosteroids. The study design has gradually evolved from observations based on a single time-point assay (pre 1992), a multiple time point assay (the 1992 OGD interim guidance on topical corticosteroids), to an assay incorporating a pilot dose response study and a pivotal bioequivalence study (the 1995 OGD guidance for topical dermatologic corticosteroids). The requirement of a particular study design for bioequivalence determination has been enforced depending upon the time when study was performed. Thus, studies performed prior to July 1, 1992, required the single-point vasoconstrictor assay, protocols executed from July 1, 1992 to Jun 2, 1995 required the multiple point assays with pharmacodynamic model fitting to each subject's vasoconstrictor response data, and studies initiated after June 2, 1995, are required to be based on the current OGD guidance for topical dermatologic corticosteroids.

C. Contents of Submission

Study Types	Yes/No?	How many?
In vitro dissolution	No	
Waiver requests	No	
Vasoconstrictor Studies	Yes	(2) Pilot and Pivotal
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Number of Operators	2
Number of Application Sites	8 (4 each arm)
ChromaMeter Used	(b) (4)
Between Subject Precision Range (%CV)	< 10.0
Between Site Precision Range (%CV)	< 10.0
Within Site Precision Range (%CV)	< 10.0
Mean Difference vs. Trainer ≤ 10% (Y/N)	Yes

Date when validation was conducted	06/27/05
Bioanalytical method is acceptable	Yes

E. In Vivo Studies

1. Pilot Dose Duration-Response Study

Study Summary, Pilot Study	
Study No.	10504909
Study Design	One-period, randomized, dose duration-response, vasoconstrictor study
Occlusion (Yes/No)?	No
No. of subjects enrolled	15
No. of subjects completing	15
No. of subjects analyzed	15
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 0 Female: 15
Reference product	CLOBEX® Lotion
Strength tested	0.05%
Amount of Dose	5 microliters
Dose Duration	0.5, 1, 3, 6, 12, 30, 60, 90 and 120 minutes

Summary of Statistical Analysis, Pilot Study, DBE Calculated		
Parameter	**ED50 (min)**	**Emax**
	7.62931	23.4756

Comment on the Pilot Dose Response Study:

1. The firm performed a pilot dose-response study on the designated reference listed drug, CLOBEX® Lotion, 0.05%. Based on a population fitting technique of the ChromaMeter dose duration-response data, the ED50 is about 7.6 min. The DBE's ED50 calculation agrees with the firm's result (see Appendix for details). Therefore, DBE agrees with the firm's choice of selecting ED50 of 6 minutes for the subsequent pivotal study.
2. For the pivotal bioequivalence study, the firm used D1, ED50 and D2 values of 3, 6, and 12 minutes, respectively.

2. Pivotal Pharmacodynamic Bioequivalence Study

Study Summary, Pivotal Study	
Study No.	10504910
Study Design	One-period, randomized, vasoconstriction study
No. of subjects enrolled	224
No. of subjects completing	224
No. of subjects analyzed	224
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 0 Female: 224
Test product	Clobetasol Propionate Lotion, 0.05%
Reference product	CLOBEX®, 0.05%
Strength tested	0.05%
Dose	5 microliters

Summary of Statistical Analysis ($AUEC_{0-24}$, Locke's Method)					
Calculated By	**N**	**Test**	**Reference**	**Point Estimate**	**90% CI**
Firm	64	8.42	8.08	104.2	87.6-124.2
DBE	64	8.42	8.08	104.2	87.6-124.2

F. Formulation

Location in appendix	Section IV.B, Page 22
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	--
Is the formulation acceptable?	Yes
If not acceptable, why?	--

G. Deficiency Comments

None.

H. Recommendations

1. The pilot dose duration-response study conducted by Novum Pharmaceutical Research Services for Alpharma USPD, Inc., on the reference product, CLOBEX®, 0.05%, Lot #WBBT, is **acceptable**.

2. The pivotal pharmacodynamic bioequivalence study conducted by Novum Pharmaceutical Research Services for Alpharma USPD, Inc., on the test product, Clobetasol Propionate Lotion, 0.05%, Lot # #X508050, comparing it with the reference product, CLOBEX®, 0.05%, Lot #WBBT, is **acceptable**.

IV. Appendix

A. Individual Study Reviews

1. Pilot Dose Duration-Response Study

a) Study Design

Study Information	
Study Number	10504909
Study Title	Dose Response of Clobetasol Propionate Lotion, 0.05%
Clinical Site	Novum Pharmaceutical Research Services, Houston, TX
Principal Investigator	Soran, Hong, M.D.
Study/Dosing Dates	10/01/05 – 10/02/05
Statistician	Novum PRS

Reference Product	CLOBEX®, 0.05%
Manufacturer	GALDERMA LABS LP
Batch/Lot No.	#WBBT
Manufacture Date	NA
Expiration Date	01, 2008
Strength	0.05%
Dosage Form	Lotion
Potency	99.2%

No. of Periods	1
No. of Groups	1
Randomization Scheme	Staggered application with synchronized removal of 9 sites plus 2 untreated sites each arm
Dose Duration Times	0.5, 1, 3, 6, 12, 30, 60, 90 and 120 minutes
Skin Blanch Reading Times	0, 2, 4, 6, 8, 10, 12, 20 and 24 hours
IRB Approval	Yes
Informed Consent	Yes
Subject Screening	Yes, healthy, non-tobacco-using females
Subjects Demographics	See Table 1
Preparation of Skin	The arm was washed with mild soap and dried approximately 2 hours prior to dosing.
Occluded or Non-Occluded	Non-occluded

Length of Confinement	During this study, the subjects were housed at the clinical facility.
Safety Monitoring	Blood pressure, pulse rate, respiratory rate and temperature measured during check-in.

Comments on Study Design: Acceptable.

b) Clinical Results

Table 1: Demographics of Study Subjects

Study No. 10504909	
	Treatment Groups
	Reference Product N = 15
Age (years)	
Mean ± SD	35.7 ± 9.2
Range	23 – 49
Groups	
< 18	0
18 – 40	8 (53%)
41 – 64	7 (47%)
65 – 75	0
> 75	0
Weight (lbs.)	
Mean ± SD	138.9 ± 18.5
Range	108 – 171
BMI	
Mean ± SD	24.4 ± 3.4
Range	18.4 – 29.1
Sex	
Female	15 (100%)
Male	0
Race	
Hispanic	11 (73%)
Caucasian	2 (13%)
Black	1 (7%)
Asian	1 (7%)
Biracial	0
Tobacco User	
Yes	0
No	15 (100%)

Table 2 Study Adverse Events

None.

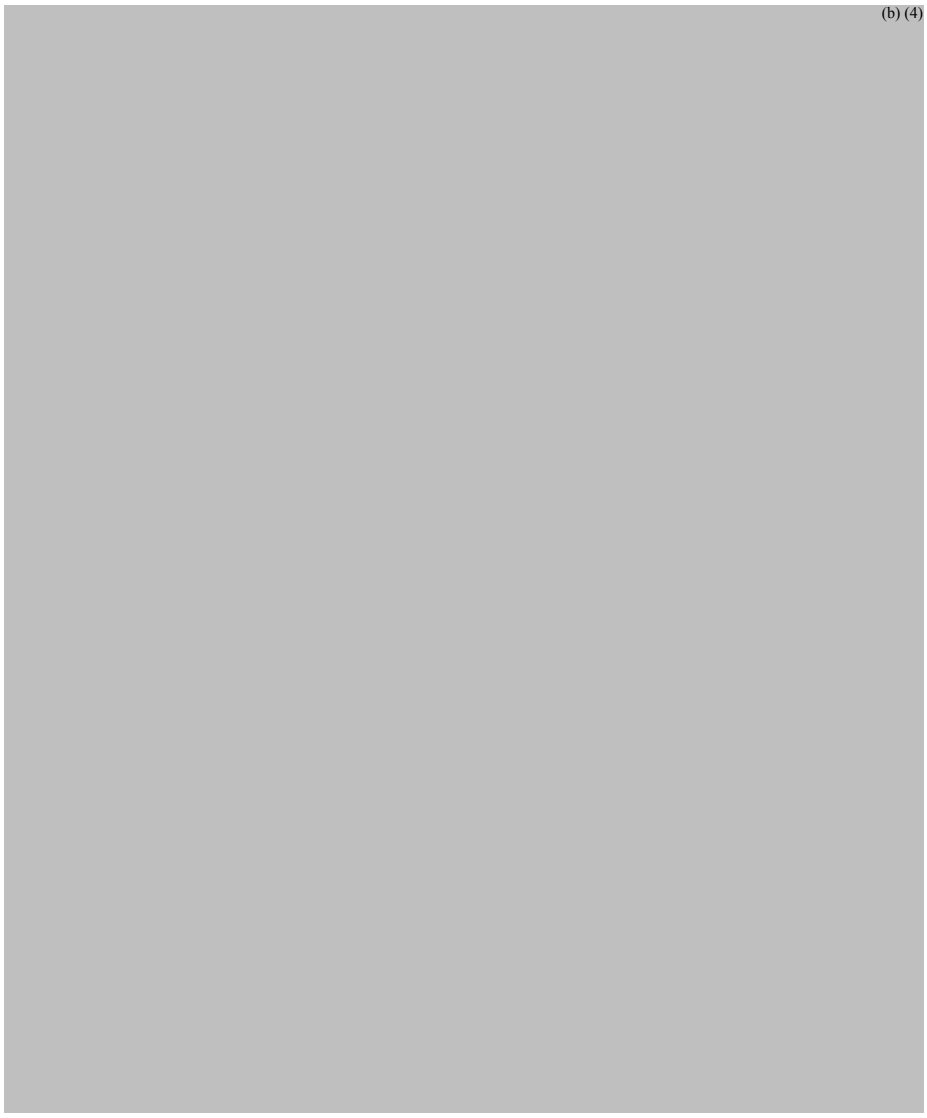
Table 3 Protocol Deviations

None.

Comments on Dropouts/Adverse Events/Protocol Deviations: Acceptable.

(b) (4)

Following this page, 2 pages withheld in full (b)(4)



2. Pivotal Pharmacodynamic Bioequivalence Study

a) Study Design

Study Information			
Study Number	10504910		
Study Title	Bioequivalence of Two Clobetasol Propionate Lotions		
Clinical Site	Novum Pharmaceutical Research Services, Houston, TX		
Principal Investigator	Soran, Hong, M.D.		
Study/Dosing Dates	Group	Subjects	Dose Date
	1	01-20	11/05/05
	2	21-40	11/10/05

	3	41-60	11/16/05
	4	61-80	11/30/05
	5	81-109	12/03/05
	6	110-135	12/10/05
	7	136-157	01/04/06
	8	158-183	01/28/06
	9	184-205	02/11/06
	10	206-224	02/25/06
Statistician	Novum PRS		

CATEGORY	Alpharma USPD, Inc. Clobetasol Propionate Lotion, 0.05%	GALDERMA LABS LP CLOBEX®, 0.05%
GENERAL		
Dosage Form	Lotion	Lotion
Route of Administration	Topical	Topical
CLINICAL SUPPLIES		
Lot #	#X508050	#WBBT
Batch Size	(b) (4)	Not Applicable
Date of Manufacture	08/2005	Not Applicable
Expiration Date	08/2007	01/2008
Packaging Component	A high density polyethylene (HDPE) bottle and a plastic closeure	Not Available
Assay	100.7%	99.2%
STUDY INFORMATION – STUDY NO. 10504910		
IRB Approval	Yes	
Dosing	11/05/05 – 02/26/06	

No. of Periods	1
No. of Groups	10
Randomization Scheme	The randomization was generated by the Biostatistics Department at Novum Pharmaceutical Research Services
Dose Duration Times (D1, ED_{50}, D2)	3 minutes, 6 minutes, 12 minutes

ChromaMeter Reading Times	0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal of the application
ChromaMeter Used	(b) (4)
IRB Approval	Yes
Informed Consent	Yes
Subject Screening	Yes, healthy, non-tobacco-using female subjects
Subjects Demographics	See Table 4
Preparation of Skin	The arm was washed with Liquid Neutrogena Facial Cleansing Formula® and dried approximately 2 hours prior to dosing.
Occluded of Non-Occluded	The treated area was NOT occluded.
Length of Confinement	During this study, the subjects were housed at the clinical facility.
Safety Monitoring	Blood pressure, pulse rate, respiratory rate and temperature measured during check-in.

Comments on Study Design: Acceptable.

b) Clinical Results

Table 4 Demographics of Study Subjects

Study No. 10504910		
	Treatment Groups	
	Test Product N = 224	Reference Product N = 224
Age (years)		
Mean ± SD	19.9 ± 1.3	19.9 ± 1.3
Range	18 – 50	18 – 50
Groups		
< 18	0	0
18 – 40	169 (75%)	169 (75%)
41 – 64	55 (25%)	55 (25%)
65 – 75	0	0
> 75	0	0
Weight (lbs.)		
Mean ± SD	114.3 ± 7.6	114.3 ± 7.6
Range	95 – 202	95 – 202
BMI		
Mean ± SD	20.7 ± 1.2	20.7 ± 1.2
Range	18.0 – 30.0	18.0 – 30.0
Sex		
Female	224 (100%)	224 (100%)
Male	0 (0%)	0 (0%)
Race		
Hispanic	175 (78%)	175 (78%)
Caucasian	30 (13%)	30 (13%)
Black	7 (3%)	7 (3%)
Asian	9 (4%)	9 (4%)
Biracial	3 (1%)	3 (1%)
Tobacco User		
Yes	0 (0%)	0 (0%)
No	224 (100%)	224 (100%)

Table 5 Dropout Information

None.

Table 6 Study Adverse Events

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Dose Response Study Study No. 10504909	Vasoconstrictor Bioequivalence Study Study No 10504910
	Reference N[1] (%[2])	Test and Reference N[1] (%[2])
Gastrointestinal Disorders		
Nausea	0	1 (0.4%)
Stomach discomfort	0	1 (0.4%)
Nervous System Disorders		
Dizziness	0	1 (0.4%)
Headache	0	2 (0.9%)
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal pain	0	1 (0.4%)
Number of subjects dosed with study drug	15	224

[1] N = Number of subjects which reported Adverse Event (AE)
[2] % (rate of occurrence) = N divided by number of subjects dosed with respective study drug.

Table 7 Protocol Deviations

One subject (#153) consumed 4 oz of coffee. This subject did not meet the D2/D1>1.25 qualification criteria and was not eligible for inclusion in the bioequivalence analysis.

c) Statistical Results

Number of Subjects Enrolled	224	
Number of Subjects Completing	224	
Number of Subjects Analyzed	64	
	Firm	**DBE**
Number of Subjects with D2/D1 ≥ 1.25	64	64
Number of Subjects Analyzed by the Locke's Method $AUEC_{0-24}$	64	64

***In Vivo* Bioequivalence Vasoconstrictor Assay Results**					
	Mean Area Under the Negative Response Curve for ChromaMeter Evaluation		Ratio %	90% Confidence Interval	
	Test	Reference	T/R	Lower %	Upper %
Firm's results	8.42	8.08	104.2	87.6	124.2
Reviewer's results	8.42	8.08	104.2	87.6	124.2

Reviewer's Comments:

1. A total of 224 healthy female subjects were dosed in the pivotal bioequivalence study and 224 subjects completed the study. There are 64 subjects who met the qualification criteria (D2/D1 ≥1.2) and were included in the BE statistical analysis.
2. DBE's calculation agrees with the firm's results.
3. The 90% confidence intervals were within the acceptable limit of 80-125%.

Summary/Conclusions, Pivotal Pharmacodynamic Bioequivalence Study:

Acceptable.

Table 8 ChromaMeter Results - Subjects with D2/D1 ≥ 1.25

Subject	D2/D1	AUEC $_{0-24}$ Ref Average	AUEC $_{0-24}$ Test Average
3	(b) (4)	-4.8575	-9.015
5		-6.1075	-19.065
6		-8.6725	-17.5025
7		-7.5525	-7.1925
9		-10.37	-20.1975
11		-15.4775	-9.935
14		-3.8125	-9.3525
22		-4.3225	-7.17
25		-7.9625	-15.655
27		-11.58	-6.49
33		-7.0775	-9.4375
36		-0.9	7.0775
47		-10.01	-4.12
48		5.1275	-1.4775
57		1.985	-7.0925
59		-11.465	-14.8725
63		-7.0875	-0.11
64		-15.285	-12.0125
67		-6.75	-0.71
68		-11.415	-7.7
69		-6.45	-5.4725
73		-26.4275	-23.715
75		-10.1425	-19.34
79		-0.975	-10.535
81		-21	-5.825
89		-5.665	-5.8875
100		-2.3075	1.475
103		-9.9375	-6.15
104		-4.7775	-0.5375
110		-2.755	-7.58
112		-15.605	-14.97
117		-10.4575	-8.635
119		-6.145	-3.08
122		-8.5275	6.3975
124		7.425	4.51
125		-13.36	-6.895
130		2.91	5.385
131		-5.235	5.455
134		-7.4725	-12.7325
138		-8.3875	-17.69
140		-10.275	-8.355
141		0.33	-3.3275
146		-5.6075	-13.47
149		-16.445	-18.97
156		-14.84	-18.0425

(b) (4)

157		-6.805	-3.4825
159		-2.15	-3.0375
168		-2.62	-14.085
169		-24.8175	-20.075
173		-15.2525	-8.9925
180		3.9875	0.895
183		8.6775	-2.11
189		-8.9875	-6.9925
191		-4.2025	-12.4075
192		-13.9625	-9.755
195		-9.8175	-12.515
199		-10.6225	-13.3625
200		-16.8025	-24.2025
201		2.565	-2.685
208		-8.7675	-6.4325
216		-11.21	-0.105
220		-26.3975	-16.63
221		-5.35	-14.46
222		-18.6625	-8.39

Table 9: Determination of $AUEC_{0-24}$ 90% CI By Locke's Method (n=64)[1]

			Arith. Mean	-8.42	-8.08	E(Xi)^2		E(TEST*REF)
ANDA	78-223		EXi	-538.84	-516.92	8044.08	7547.04	6347.46
Date	23-Jan-2007		(EXi)^2	290351 24	267206.29			
Reviewer:	BingLi		((EXi)^2)/n	4536.74	4175.10			
AVETest	-8.42							
AVEREF	-8.08		Exti/EXri	1.04241				
T/R	1.042		(Exti/Exri)^2	1.09				
DTR	31.67		DTT/DRR	1.04				
DRR	53.52		DTR/DRR	0.59				
DTT	55.67							
Inta Sub Var (%)	-59.28		SUBJ	TEST	REF	(TEST)^2	(REF)^2	(TEST)*(REF)
			3	-9.015	-4.8575	81.27	23.60	43.79
K	0.87		5	-19.065	-6.1075	363.47	37.30	116.44
SQRT(K)	0.93		6	-17.5025	-8.6725	306.34	75.21	151.79
W	0.02		7	-7.1925	-7.5525	51.73	57.04	54.32
n	64		9	-20.1975	-10.37	407.94	107.54	209.45
t	1.669		11	-9.935	-15.4775	98.70	239.55	153.77
t^2	2.79		14	-9.3525	-3.8125	87.47	14.54	35.66
Gr	0.04		22	-7.17	-4.3225	51.41	18.68	30.99
DRR*W	0.84		25	-15.655	-7.9625	245.08	63.40	124.65
SQRT(DRR*W)	0.91		27	-6.49	-11.58	42.12	134.10	75.15
			33	-9.4375	-7.0775	89.07	50.09	66.79
-CINT	1.242		36	7.0775	-0.9	50.09	0.81	-6.37
+CINT	0.876		47	-4.12	-10.01	16.97	100.20	41.24
			48	-1.4775	5.1275	2.18	26.29	-7.58
90% CI:	124.17		57	-7.0925	1.985	50.30	3 94	-14.08
	87.65		59	-14.8725	-11.465	221.19	131.45	170.51
			63	-0.11	-7.0875	0.01	50.23	0.78
			64	-12.0125	-15.285	144.30	233.63	183.61
			67	-0.71	-6.75	0.50	45.56	4.79
			68	-7.7	-11.415	59.29	130.30	87.90
			69	-5.4725	-6.45	29.95	41.60	35.30
			73	-23.715	-26.4275	562.40	698.41	626.73
			75	-19.34	-10.1425	374.04	102.87	196.16
			79	-10.535	-0.975	110.99	0.95	10.27
			81	-5.825	-21	33.93	441.00	122.33

			89	-5.8875	-5.665		34.66	32.09	33.35
			100	1.475	-2.3075		2.18	5.32	-3.40
			103	-6.15	-9.9375		37.82	98.75	61.12
			104	-0.5375	-4.7775		0.29	22.82	2.57
			110	-7.58	-2.755		57.46	7 59	20.88
			112	-14.97	-15.605		224.10	243.52	233.61
			117	-8.635	-10.4575		74.56	109.36	90.30
			119	-3.08	-6.145		9.49	37.76	18.93
			122	6.3975	-8.5275		40.93	72.72	-54.55
			124	4.51	7.425		20.34	55.13	33.49
			125	-6.895	-13.36		47.54	178.49	92.12
			130	5.385	2.91		29.00	8.47	15.67
			131	5.455	-5.235		29.76	27.41	-28.56
			134	-12.7325	-7.4725		162.12	55.84	95.14
			138	-17.69	-8.3875		312.94	70.35	148.37
			140	-8.355	-10.275		69.81	105.58	85.85
			141	-3.3275	0.33		11.07	0 11	-1.10
			146	-13.47	-5.6075		181.44	31.44	75.53
			149	-18.97	-16.445		359.86	270.44	311.96
			156	-18.0425	-14.84		325.53	220.23	267.75
			157	-3.4825	-6.805		12.13	46.31	23.70
			159	-3.0375	-2.15		9.23	4.62	6.53
			168	-14.085	-2.62		198.39	6.86	36.90
			169	-20.075	-24.8175		403.01	615.91	498.21
			173	-8.9925	-15.2525		80.87	232.64	137.16
			180	0.895	3.9875		0.80	15.90	3.57
			183	-2.11	8.6775		4.45	75.30	-18.31
			189	-6.9925	-8.9875		48.90	80.78	62.85
			191	-12.4075	-4.2025		153.95	17.66	52.14
			192	-9.755	-13.9625		95.16	194.95	136.20
			195	-12.515	-9.8175		156.63	96.38	122.87
			199	-13.3625	-10.6225		178.56	112.84	141.94
			200	-24.2025	-16.8025		585.76	282.32	406.66
			201	-2.685	2.565		7.21	6.58	-6.89
			208	-6.4325	-8.7675		41.38	76.87	56.40
			216	-0.105	-11.21		0.01	125.66	1.18
			220	-16.63	-26.3975		276.56	696.83	438.99
			221	-14.46	-5.35		209.09	28.62	77.36
			222	-8.39	-18.6625		70.39	348.29	156.58

E: Sum
D: Sigma hat in Locke's method
n: Number of subjects
t: Student's t value for d.f. = n-1, (The firm used t=1.669 in this study)

[1.] Locke, C.S., An exact confidence interval from untransformed data for the ratio of two formulation means. J. Pharmacokinet. Biopharm. 1984 Dec; 12(6):649-655

B. Formulation Data

Ingredient	Amount / Gram	Amount (%)
Clobetasol Propionate USP	0.0005 g	0.05%
Carbomer 940 NF		(b) (4)
Propylene Glycol USP		
Hypromellose USP (b) (4)		
Mineral Oil USP		
Polyoxyethylene Glycol 300 Isostearate		
Polysorbate 80 NF		
Sodium Hydroxide NF		
Purified Water USP		

RLD formulation (obtains from NDA 21-535 review, review of the original submission on Sept. 22, 2002, by Division of Dermatologic and Dental Drug Products, **Not to Be Released under FOI**)

Ingredient	% (w/w)
Clobetasol propionate, USP	0.05
Hydroxypropyl methyl cellulose, USP	(b) (4)
PEG (b) (4) Isostearate	
Carbomer (b) (4) NF	
Mineral Oil, USP	
Propylene glycol, USP	
Sodium Hydroxide, NF	
Purified water	q.s.

Reviewer's Comments on Formulation:

1. The inactive ingredients in the formulation are within the acceptable IIG range. (V:\Firmsam\Alpharma.usp\LTRS&REV\78223.CHK.DOC)
2. The formulation is acceptable.

BIOEQUIVALENCE COMMENTS

ANDA: 78-223 APPLICANT: Alpharma USPD, Inc.

DRUG PRODUCT: Clobetasol Propionate Lotion, 0.05%

The Division of Bioequivalence has completed its review and has no further questions at this time.

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
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-223

BIOEQUIVALENCY - COMMENTS Submission date: May 19, 2005

1. Pilot Study (STU) Strengths: 0.05% lotion
   Novum PRS Outcome: AC

2. Pivotal Study (STU) Strengths: 0.05% lotion
   Novum PRS Outcome: AC

Outcome Decisions: AC - Acceptable

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

/s/

Bing Li
2/14/2007 11:33:36 AM
BIOPHARMACEUTICS

Moheb H. Makary
2/14/2007 11:35:22 AM
BIOPHARMACEUTICS

Dale Conner
2/15/2007 10:18:33 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078223

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

actavis
creating value in pharmaceuticals

ORIGINAL ANDA

March 24, 2006

UPS OVERNIGHT COURIER

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place, MPN 4, HFD-600
Rockville, MD 20855

RE: Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler,

In accordance with the regulations promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act as amended, Alpharma USPD Inc. (a subsidiary of Actavis Group) is submitting this original Abbreviated New Drug Application (Archival and Review Copies) for Clobetasol Propionate Lotion, 0.05%.

This Abbreviated New Drug Application has been prepared in accordance with 21 CFR 314.94 and contains a total of **17 volumes**, comprising the Archival Copy and Review Copy (chemistry, manufacturing and controls review part and bioavailability/bioequivalence review part).

Clobetasol Propionate raw material is the subject of a monograph in the USP, however additional in-house test methods have been developed for the drug substance. Clobetasol Propionate Lotion drug product is not the subject of a monograph in the USP. Therefore, in-house test methods have been developed for the analysis of the bulk drug product, packaged finished product and stability samples. These test methods have been fully validated with respect to the API and drug product. Please note that, although the tests specific to the API and the drug product are performed using in-house methods, certain general tests are conducted using methods from the general chapters of USP. These General In-house Test Methods are also provided. *Alpharma acknowledges that in the event of a dispute, USP general chapter methods will be used as the regulatory methods.*

Alpharma acknowledges the requirement for analytical methods validation by the FDA District Laboratory. We commit to working with the District Laboratory to resolve any issues identified during the validation process should ANDA approval be granted prior to completion of this exercise.

Purepac Pharmaceutical Co.
Alpharma USPD Inc.
Regulatory Affairs Department
One New England Avenue
Piscataway, NJ 08854 USA
t 732 465 3632
f 732 465 3731
www.actavis.com

Accordingly, two (2) separately bound copies of the analytical methods and related descriptive information are provided with this original ANDA.

Please note that in addition to the draft labeling submitted in **Section V**, the electronic submission of the labeling is included in accordance with the final rule titled "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format", which became effective June 8, 2004.

In conjunction with this submission, Alpharma USPD has provided a Field Copy of this application to our district office in accordance with 21 CFR 314.94(d)(5). Please note that the required Field Copy Certification is contained in **Section XXI** of our abbreviated application. In addition, the following certification is provided in this submission:

- A certification in accordance with Section 306(K) of the Federal Food Drug and Cosmetic Act as amended by the "Generic Drug Enforcement Act" **(Section XX).**

- A certification regarding the financial interests and arrangements of the clinical investigators responsible for the treatment or evaluation of research subjects enrolled in the bioequivalence studies supporting this application **(Section VI).**

Additionally, Alpharma USPD acknowledges that all firms referenced in this ANDA, with respect to the manufacture and testing of the subject drug product, must be in compliance with current good manufacturing practices at the time of approval. A signed acknowledgment is contained in **Section IX** of this application. Alpharma USPD also acknowledges that all DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA.

Alpharma USPD Inc. trusts that you will find this application complete and well organized, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (732) 465-3631 or fax number (732) 465-3731.

Sincerely,
ALPHARMA USPD INC.

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/sb
Enclosures

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NA 1.

ORIGINAL

dmy 6/2/2006

PATENT AMENDMENT

UPS OVERNIGHT COURIER

May 22, 2006

XP

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place, MPN 4, HFD-600
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler,

Reference is made to our March 24, 2006 submission of an Abbreviated New Drug Application, ANDA # 78-223 for Clobetasol Propionate Lotion, 0.05%. Reference is also made to the facsimile dated May 18, 2006 acknowledging the receipt of this application.

In accordance with 21 CFR 314.95(b), Alpharma USPD, Inc. is amending the subject application to certify that the requirements stated in 21 CFR 314.95(a) and 21 CFR 314.95(c) have been satisfied. On May 22, 2006, Alpharma USPD, Inc. notified the patent holder, Galderma S.A., and the holder of the approved application, Galderma Labs LP that Alpharma USPD, Inc. had submitted an ANDA containing a paragraph IV certification. The contents of the notice complied with the requirements set forth in 21 CFR 314.95(c).

Please be advised that once confirmation of receipt from Galderma S.A. and Galderma Labs LP, have been received by Alpharma USPD, Inc., another patent amendment will be sent containing a copy of this confirmation.

If there are any questions concerning this amendment, please contact the undersigned at telephone number (908) 659-2595 or fax number (908) 659-2250.

Sincerely,
ALPHARMA USPD, INC.

Christopher Uhe for

Janak Jadeja, R. Ph.
Director, Regulatory Affairs

RECEIVED
MAY 23 2006
OGD / CDER

JJ/sb
Enclosure

Purepac Pharmaceutical Co.
Alpharma USPD Inc.
Regulatory Affairs Department
One New England Avenue
Piscataway, NJ 08854 USA
t 732 465 3632
f 732 465 3731
www.actavis.com

ORIGINAL

UPS OVERNIGHT COURIER

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place
MPN 4, HFD-600
Rockville, MD 20855

CORRESPONDENCE TO FILE

N/A

May 26, 2006

78-223

RE: Highlighted ANDA in the appended list

Dear Mr. Buehler,

As per the telephone conversation that took place on May 22, 2006 between Mr. Martin Shimer, Branch Chief, Regulatory Support Branch at OGD and Janak Jadeja, this correspondence provides for the company name change and new address of our Regulatory Affairs office as follows:

Company name change:
On December 20, 2005, the Actavis Group, through its wholly owned subsidiary Actavis Inc., assumed legal ownership of Alpharma USPD from Alpharma Inc. Subsequently, Actavis Inc. has re-named Alpharma USPD to Actavis Mid Atlantic LLC effective May 15, 2006. Please be advised that the physical entity of Alpharma USPD (former applicant name) remains unchanged under the new company name.

Regulatory Affairs Office address:
Effective immediately, our Regulatory Affairs office has relocated to the following address:

Actavis Mid Atlantic LLC
200 Elmora Avenue
Elizabeth, New Jersey 07207
Phone number (908) 659-2595
Fax number (908) 659-2250

Actavis Mid Atlantic LLC requests the Agency to update their records accordingly. A list of ANDAs, with affected application highlighted, is appended with this letter. Should any question arise, please do not hesitate contacting me at above listed phone/fax number.

Sincerely,
ACTAVIS Mid Atlantic LLC

Janak Jadeja, R.Ph.
Director
Regulatory Affairs

RECEIVED
MAY 30 2006
OGD / CDER

AFFECTED ANDAs

ANDA #	STATUS	PRODUCT NAME
70-885	Approved	Betamethasone Dipropionate Cream USP, eq. 0.05% (base)
71-012	Approved	Betamethasone Dipropionate Ointment USP, eq. 0.05% (base)
74-304	Approved	Betamethasone Dipropionate Ointment USP, eq. 0.05% (base) (Augmented)
70-050	Approved	Betamethasone Valerate Cream USP, eq. 0.1% (base)
70-051	Approved	Betamethasone Valerate Ointment USP, eq. 0.1% (base)
74-139	Approved	Clobetasol Propionate Cream USP, 0.05%
78-223	Pending Approval	Clobetasol Propionate Lotion, 0.05%
74-128	Approved	Clobetasol Propionate Ointment USP, 0.05%
76-002	Approved	Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)
74-165	Approved	Clotrimazole Vaginal Cream USP, 1%
73-085	Approved	Fluocinonide Cream USP, 0.05%
74-204	Approved	Fluocinonide Cream USP, 0.05% (Emulsified Base)
		(b) (4)
77-109	Approved	Halobetasol Propionate Ointment, 0.05%
87-795	Approved	Hydrocortisone Cream USP, 1%
89-682	Approved	Hydrocortisone Cream USP, 2.5%
87-796	Approved	Hydrocortisone Ointment USP, 1%
74-926	Approved	M-Zole 3 Combination Pack (Miconazole Nitrate Vaginal Suppositories USP, 200 mg and Miconazole Nitrate Cream, 2%)
74-586	Approved	M-Zole 7 Combination Pack (Miconazole Nitrate Vaginal Suppositories USP, 100 mg and Miconazole Nitrate Cream, 2%)
74-164	Approved	Miconazole Nitrate Vaginal Cream, 2%
73-507	Approved	Miconazole Nitrate Vaginal Suppositories USP, 100 mg
73-508	Approved	Miconazole Nitrate Vaginal Suppositories USP, 200 mg
62-949	Approved	Nystatin Cream USP, 100,000 units/g
62-840	Approved	Nystatin Ointment USP, 100,000 units/g

A2-1

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ORIGINAL

Sued re: PIV Certification. AMY

PATENT AMENDMENT

UPS OVERNIGHT COURIER

XP

July 11, 2006

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place
MPN 4, HFD-600
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to our March 24, 2006 submission of an Abbreviated New Drug Application, ANDA #78-223 for Clobetasol Propionate Lotion, 0.05%. Further reference is made to our patent amendment dated May 22, 2006 that was submitted in accordance with 21 CFR 314.95(b) which included the following:

- Certification from Actavis Mid Atlantic LLC (formerly Alpharma USPD, Inc.) that Galderma S.A., the holder of U.S. patent 6,106,848, and Galderma Labs LP, the holder of the approved application for reference listed drug product, Clobex™ Topical Lotion, 0.05%, were notified that our firm filed an ANDA containing a paragraph IV certification.

On May 22, 2006, Actavis Mid Atlantic LLC notified Galderma S.A. and Galderma Labs LP that Actavis Mid Atlantic LLC had submitted an ANDA containing a paragraph IV certification. Galderma S.A. is the holder of U.S. Patent 6,106,848. Galderma Labs LP is the holder of the approved application for the reference listed drug product Clobex™ Topical Lotion, 0.05%. The contents of the notice complied with the requirement set forth in 21 CFR 314.95(c).

This correspondence and its enclosures are intended to fulfill the requirements set forth in 21 CFR 314.95(e), 314.107(f)(1) and 314.107(f)(2) regarding documentation of receipt of notice, computation of the 45-day clock and notification of legal action. Enclosed please find the following:

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

314.95(e)

1) **Documentation confirming receipt of notice by the patent holder, Galderma S.A.:**

Actavis Mid Atlantic LLC sent notification to Galderma S.A. on May 22, 2006 via UPS Overnight Courier. Pursuant to 21 CFR 314.95(e), Actavis Mid Atlantic LLC is providing as documentation of receipt of notice, a copy of the UPS Tracking Confirmation Report dated June 1, 2006. The Tracking Confirmation Report shows that the notice was delivered on May 24, 2006 and is provided in Section 1. Please be advised that on May 19, 2006, Actavis had sent a written request to provide the notice via alternate means since Galderma S.A. is located outside of the United States. On May 22, 2006, Mr. Martin Shimer, Branch Chief, Regulatory Support Branch at OGD verbally confirmed acceptance of sending the notice via UPS Overnight Courier.

2) **Documentation confirming receipt of notice by the application holder, Galderma Labs LP:**

Actavis Mid Atlantic LLC sent notification to Galderma Labs LP on May 22, 2006 via U.S. Postal Service Domestic Certified Mail. Pursuant to 21 CFR 314.95(e), Actavis Mid Atlantic LLC is providing as documentation of receipt of notice, a copy of the certified mail return receipt from Galderma Labs LP dated May 25, 2006 in Section 2.

314.107(f)(1)

In accordance with 21 CFR 314.107(f)(1), the 45-day period expired on July 10, 2006.

314.107(f)(2)

Pursuant to 21 CFR 314.107(f)(2) and the provisions of our letter of ANDA filing acceptance dated May 18, 2006, Actavis Mid Atlantic LLC hereby certifies that Galderma Labs LP, holder of the approved application for the reference listed drug product Clobex™ Topical Lotion, 0.05% and Galderma S.A., the holder of U.S. Patent 6,106,848, has filed a complaint of patent infringement against our firm relative to the patent 6,106,848 ("the '848 patent") on June 30, 2006.

The complaint of patent infringement for the '848 patent was filed with the United States District Court for the Northern District of Texas Fort Worth Division within the 45-day period as provided for in Section 505(j)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act. A copy of the complaint is provided in Section 2 of this application.

If there are any questions concerning this amendment, please contact the undersigned at telephone number (908) 659-2595 or fax number (908) 659-2250.

Sincerely,

ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/cu
Enclosures

A2.1

GALDERMA
USA

ORIG AMENDMENT
N-000-MC
7/20/06,
Notice of litigation filed 7/5/06 for patent '848. Filed within 45 day time period per NDA holder, but cannot confirm until RR are sent to office.

GALDERMA
LABORATORIES, L.P.
14501 N. Freeway
Fort Worth,
TEXAS
76177
Tel: (817) 961-5000

July 12, 2006

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place, MPN 4, HFD-600
Rockville, MD 20855

Re: **Clobetasol Proprionate Lotion, 0.05%**
Actavis Mid Atlantic LLC
ANDA No. 78-223

Dear Mr. Buehler,

Galderma Laboratories, L.P. ("Galderma") is the exclusive marketing agent for Galderma S.A. for Clobex® Topical Lotion, 0.05% pursuant to approved New Drug Application No. 021535. On May 25, 2006, Galderma received a Paragraph IV Certification Letter (the "Certification Letter") from Actavis Mid Atlantic, LLC ("Actavis") relating to ANDA No. 78-223 (the "ANDA") for Clobetasol Proprionate Lotion, 0.05%.

Galderma hereby certifies that, within forty-five days of its receipt of the Certification Letter, it filed suit against Actavis under Cause No. 4-06CV-471-Y (the "Suit"), in the United States District Court for the Northern District of Texas, Fort Worth Division. A file-stamped copy of Galderma's Original Complaint is enclosed.

In the Suit, Galderma contends that Actavis infringed United States Patent No. 6,106,848 by filing the ANDA. Therefore, pursuant to 21 U.S.C. § 355, the Food and Drug Administration's approval (if any) of the ANDA shall not be made effective until the expiration of a thirty-month period beginning on May 25, 2006 (the date of receipt of the Paragraph IV Certification Letter) or such shorter or longer period as the court may order.

If you have any questions, please contact me.

Best regards,

Quintin Cassady
Vice President and General Counsel

Enc.

cc: Terri Nataline, Esq. (with enclosure)
Director, Intellectual Property
Actavis Mid Atlantic LLC
200 Elmora Avenue
Elizabeth, NJ 07207

Telephone Fax

ANDA 78-233

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301- 827-7345

TO: Alpharma USPD

TEL: 732 465-3631

ATTN: Janak Jadeja

FAX: 732 465-3731

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 clobetasol propionate lotion

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 78-223

Date of Submission: **March 24, 2006**

Applicant's Name: Alpharma USPD Inc.

Established Name: Clobetasol Propionate Lotion, 0.05%.

Labeling Deficiencies:

1. **GENERAL COMMENT: [ALL LABELING] -** Revise your storage temperature on your labels and labeling to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]".
2. **CONTAINER** (30mL, 59 mL) - See General Comment.
3. **CARTON** (30 mL, 59 mL) – See General Comment.
4. **PROFESSIONAL INSERT -** See general Comment.
5. **PATIENT INFORMATION:** Satisfactory in Draft.

   Please ensure that the instructions for use are provided as a separate labeling piece within the carton or that they may be separated from the physician labeling as a distinct piece.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of 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
11/29/2006 01:16:05 PM
for Wm Peter Rickman

MINOR AMENDMENT

ANDA 78-223

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: Actavis Mid Atlantic (Formerly Alpharma USPD)

TEL: 908-659-2432

ATTN: Janak Jadeja

FAX: 908-659-2440

FROM: Rosalyn Adigun, Pharm.D.

PROJECT MANAGER: (301)-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 24, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Lotion, 0.05%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (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 attached

36. Chemistry Comments to be provided to the Applicant

ANDA: 78-223 APPLICANT: Actavis Mid Atlantic LLC

DRUG PRODUCT: Clobetasol Propionate Lotion, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please evaluate [redacted] (b) (4)

2. Please qualify [redacted] (b) (4)

3. Please include [redacted] (b) (4)

4. DMF [redacted] (b) (4) has been reviewed and found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has notified you that they have answered their deficiencies.

5. Please include [redacted] (b) (4)

6. Please provide [redacted] (b) (4)

7. Please include [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 provide all available long-term drug product stability data.

2. USP methods are the regulatory methods for the drug substance. In the event of a dispute, the USP methods will prevail.

3. Information related to the labeling and bioequivalency is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

4. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

5. On page162 you stated that the specification for unknown related compounds is set in agreement with the IT (identification threshold) of 0.10% prescribed in ICH Q3A (R) for drug substances with a maximum daily dose of ≤2 g/day. The statement "… with a maximum daily dose of ≤2 g/day" is incorrect. The correct answer should be ≤1 g/day.

Sincerely yours,

Rashmikant 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/

James Fan
12/1/2006 11:18:36 AM

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MINOR AMENDMENT & GRATUITOUS INFORMATION

UPS OVERNIGHT COURIER

June 15, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7519 Standish Place, MPN 4, HFD-600
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's (formerly Alpharma USPD, Inc.) March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Further reference is made to the Agency's chemistry deficiency letter dated December 1, 2006.

Gratuitous Information:

Please note, in addition to the Agency's comments and our firm's response as seen on the following pages, Actavis Mid Atlantic LLC is providing pertinent information for the addition of a 4 oz package size.

In support of the new package size, Actavis manufactured Bulk Batch #600/613-L665 / Packaged Lot #s X603109 (1 oz) and X604035 (4 oz) for Clobetasol Propionate Lotion, 0.05% utilizing Master Batch Formula/Standard Operating Instructions (MBF/SOI) #600613/800.0. Please note, the bulk batch manufactured represents the same formulation and manufacturing process as our current proposed commercial size batch.

Included for your review is the executed batch record and packaging documentation for Bulk Batch #600/613-L665. All supporting quality control specifications, test results, packaging materials, labeling, testing monograph and stability data are also provided.

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

Following this page, 6 pages withheld in full (b)(4)

(b) (4)

Please refer to the attached Table of Contents for a complete listing of information supporting the minor amendment and gratuitous information.

In addition, the labeling portion of this amendment is being provided in electronic format on *one (1)* CD-ROM, with a total approximate size of 6 megabytes. Actavis affirms that this electronic submission was verified to be virus free using TrendMicro Office Scan Corporate Edition 7.3 on June 15, 2007.

In conjunction with this submission, Actavis is providing a Field Copy of this application to our local District Office in accordance with 21 CFR 314.96(b). Actavis certifies that the Field Copy is a true copy of the technical section described in 21 CFR 314.94(a)(9) contained in the Archival and Review Copies of this submission.

This concludes our **MINOR AMENDMENT** in response to your chemistry deficiency letter of December 1, 2006. Actavis Mid Atlantic LLC trusts you will find this amendment complete and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/sb
Enclosures

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AMENDMENT
(LABELING)

UPS OVERNIGHT COURIER

January 2, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
7519 Standish Place
MPN 4, HFD-600
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's (formerly Alpharma USPD, Inc.) March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Further reference is made to the Agency's labeling deficiency letter dated November 29, 2006.

Actavis Mid Atlantic LLC is amending the above-referenced application to provide for revised labeling in accordance with the above noted letter.

This amendment is being provided in electronic format on *one (1)* CD-ROM. Actavis affirms that this electronic submission is free from viruses. This was confirmed through virus checks performed using TrendMicro Office Scan Corporate Edition 7.3 on January 2, 2008.

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

Contained on this CD-ROM for your review are pdf files of our proposed labeling formatted as for final print and side-by-side comparisons with all differences annotated, and explained.

If this meets with your approval, please consider this as final printed labeling.

Actavis has provided the following documents in paper format with original signatures in addition to the electronic media:

1) Cover letter
2) FDA Form 356h

Actavis Mid Atlantic LLC trusts that you will find this amendment complete and looks forward to the review process. If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/fp

Enclosures

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TELEPHONE AMENDMENT

UPS OVERNIGHT COURIER

April 8, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7500 Standish Place, MPN 2
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Further reference is made to the Agency's chemistry deficiency letter dated March 31, 2008. Your comments are provided in bold type, followed by our firm's response.

A. Deficiencies:

(b) (4)

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

Following this page, 1 page withheld in full (b)(4)

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

Agency's Comments

1. Please provide all available long-term drug product stability data.

Actavis' Response

Available long-term room temperature stability data is provided in Section 1 of this amendment. This data includes the 24-month test station for lots X508051 (1 oz.) and X508050 (2 oz.) and the 18-month test station for lots X603109 (1 oz.) and X604035 (4 oz.).

The entire submission, which includes the cover letter, 356h Form and 3674 Form is provided on *one (1)* CD-ROM. The content of the CD was verified to be virus free using TrendMicro Offices Scan Corporate Edition 7.3 on the date of submission. In addition to the CD-ROM, Actavis is also providing the following documents in paper format with original signatures:

- Cover Letter
- FDA Form 356h
- FDA Form 3674

This concludes our **TELEPHONE AMENDMENT** in response to your chemistry deficiency letter of March 31, 2008. Actavis Mid Atlantic LLC trusts you will find this amendment complete and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/cu
Enclosures

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AMENDMENT
(LABELING)

UPS OVERNIGHT COURIER

August 25, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
OGD Document Control Room
7500 Standish Place, MPN 2
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Further reference is made to our submission dated June 15, 2007, for the addition of a 4 ounce package size.

Actavis Mid Atlantic LLC is amending the above-referenced application to provide for revised package insert labeling, which reflects a correction to the patient information leaflet section. In the June 15, 2007 amendment, Actavis revised the How Supplied section of the package insert to incorporate the 4 ounce bottle size information, but inadvertently did not revise the patient information leaflet section to reflect this new information.

This amendment is being provided in electronic format on *one (1)* CD-ROM. Actavis affirms that this electronic submission is free from viruses. This was confirmed through virus checks performed using TrendMicro Office Scan Corporate Edition 7.3 on the day of submission.

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

Contained on this CD-ROM for your review are pdf files of our proposed labeling formatted as for final print and a side-by-side comparison with all differences annotated, and explained.

If this meets with your approval, please consider this as final printed labeling.

Actavis has provided the following documents in paper format with original signatures in addition to the electronic media:

1) Cover letter
2) FDA Form 356h

Actavis Mid Atlantic LLC trusts that you will find this amendment complete and looks forward to the review process. If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Francesca Visciotta / for

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/fp

Enclosures

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MINOR AMENDMENT-FINAL APPROVAL REQUESTED

UPS OVERNIGHT COURIER

October 10, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7500 Standish Place, MPN 2
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Further reference is made to the Agency's May 29, 2008 letter stating that this application is tentatively approved. Actavis hereby submits this Minor Amendment-Final Approval Requested to the referenced Abbreviated New Drug Application in accordance with the provisions in the tentative approval letter dated May 29, 2008.

This amendment is being submitted in anticipation of the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii). The expiration date has been determined to be November 24, 2008 based on the following information:

Our original ANDA #78-223, for Clobetasol Propionate Lotion, 0.05%, containing a Paragraph IV patent certification, was submitted on March 24, 2006. The subject application was found acceptable for filing (received) by the agency as of March 27, 2006. Notification of Actavis' paragraph IV certification was delivered to Galderma S.A. on May 24, 2006 and to Galderma Laboratories L.P. (collectively "Galderma") on May 25, 2006.[1] Therefore, the 30-month period is set to expire on November 24, 2008.

---

[1] On June 30, 2006, Galderma filed a complaint of patent of infringement against Actavis based on its paragraph IV certification filed in this ANDA. That lawsuit, entitled *Galderma Laboratories L.P. and Galderma S.A. v. Actavis Mid Atlantic LLC*, Civil Action No. 4-06CV-471-Y is currently pending before the U.S. District Court for the Northern District of Texas. No trial date has been set. Actavis will provide the Agency with a copy of any final court decision should one issue in this case.

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

Furthermore, based on the FDA's Paragraph IV list, which identifies the first PIV Clobetasol Propionate Lotion application submission date as March 27, 2006, Actavis believes that our ANDA was the first submitted containing a Paragraph IV certification. Accordingly, Actavis may be entitled to a 180-day period of exclusivity. In light of this potential exclusivity, Actavis is actively pursuing final approval of the subject application upon the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii).

In accordance with the requirements stated in the May 29, 2008 Tentative Approval letter, Actavis is providing the following updated chemistry, manufacturing and controls (CMC) information in this Minor Amendment:

- Revised raw material testing monograph and specification for Clobetasol Propionate drug substance along with a detailed list of changes is provided in Section 1. Actavis [redacted] (b) (4)

- Information regarding the inactive ingredients utilized in Clobetasol Propionate Lotion, 0.05% is provided in Section 2. The information includes updated monographs and specifications, residual solvent evaluations in accordance with USP General Chapter <467>, and a new manufacturer, [redacted] (b) (4) for the excipient Sodium Hydroxide NF.

- Updated information and corresponding documentation, including a detailed list of changes, regarding our revised finished product monograph and specifications for Clobetasol Propionate Lotion, 0.05% is provided in Section 3. Changes to the finished product monograph and specifications were necessary due to the following recently identified issues:

  Analytical Methods:

  Differences in chromatography were observed during laboratory transfer activities for the tentatively approved assay and related substance methods. To minimize these chromatographic differences, revised assay and related substance methods, with improved robustness and specificity, have been developed and fully validated. Furthermore, data has been generated that demonstrates that the new methods produce equivalent results and exhibit superior robustness when compared to the tentatively approved methods.

  Due to these method improvements, Actavis has observed [redacted] (b) (4)

(b) (4)

The revised product monograph, incorporating the proposed methods, validation reports, and rationale for the changes to the methods are included in Section 3.

Residual Solvents:

(b) (4)

. Please refer to Section 3 for a copy of the Residual Solvent Evaluation Report along with Actavis' revised finished product specifications.

- Information regarding a new cap manufacturer, (b) (4) for the 2 oz and 4 oz container/closure system is included in Section 4. Please be advised that there are no changes to the resin or colorant.

- Updated information and corresponding documentation regarding our revised commercial Master Batch Formula/Standard Operating Instructions and Master Packaging Records along with a detailed list of the minor changes are included in Section 5.

- Updated long-term room temperature stability data through the twenty-four month test station is included in Section 6.

Please refer to the attached Table of Contents for a complete listing of information supporting this amendment.

The entire submission is provided on *one (1)* CD-ROM. The content of the CD was verified to be virus free using TrendMicro Offices Scan Corporate Edition 7.3 on the date of submission. In addition to the CD-ROM, Actavis is also providing the cover letter and 356h in paper format with original signatures.

This concludes our **MINOR AMENDMENT-FINAL APPROVAL REQUESTED** for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Actavis Mid Atlantic LLC trusts that you will find this amendment complete and looks forward to Final Approval of its Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

JJ/cu
Enclosures

ORIGINAL

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TELEPHONE AMENDMENT

UPS OVERNIGHT COURIER

November 18, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7500 Standish Place, MPN 2
Rockville, MD 20855

ORIG AMENDMENT
N-AM

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Reference is also made to Actavis' October 10, 2008 Minor Amendment – Request for Final Approval. Further reference is made to the November 18, 2008 telephone conversation between Dr. Liang-Lii Huang, Chemistry Reviewer at OGD and Christopher Uhrin of Actavis.

As per the Agency's request, Actavis commits to placing the first batch of Clobetasol Propionate Lotion, 0.05% packaged in the 2 oz. and 4 oz. bottles utilizing the new cap (b) (4) on room temperature stability. The stability data will be provided in the Annual Report.

This concludes our **TELEPHONE AMENDMENT** for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Actavis Mid Atlantic LLC trusts that you will find this amendment complete and looks forward to Final Approval of its Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2595.

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

NOV 20 2008

JJ/cu

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

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TELEPHONE AMENDMENT

UPS OVERNIGHT COURIER

November 25, 2008

ORIG AMENDMENT

N/A 80

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7500 Standish Place, MPN 2
Rockville, MD 20855

RE: ANDA # 78-223
Clobetasol Propionate Lotion, 0.05%

Dear Mr. Buehler:

Reference is made to Actavis Mid Atlantic LLC's March 24, 2006 submission of an Abbreviated New Drug Application for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Reference is also made to Actavis' October 10, 2008 Minor Amendment – Request for Final Approval. Further reference is made to the November 25, 2008 telephone conversation between Martin Shimer, Branch Chief, Regulatory Support Branch at OGD and Actavis.

As per the Agency's request, Actavis is providing the status of the civil action filed with the United States District Court for the Northern District of Texas Fort Worth Division against Actavis Mid Atlantic LLC, court case 06-cv-00471-Y. Actavis confirms via this Telephone Amendment that litigation for court case 06-cv-00471-Y is still pending and no trial date has been set. To date, Galderma has not sought injunctive relief that would prevent Actavis from receiving final approval of its Clobetasol Propionate Lotion ANDA.

This concludes our **TELEPHONE AMENDMENT** for Clobetasol Propionate Lotion, 0.05%, ANDA #78-223. Actavis Mid Atlantic LLC trusts that you will find this amendment complete and looks forward to Final Approval of its Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2595.

RECEIVED
NOV 26 2008
OGD

Sincerely,
ACTAVIS MID ATLANTIC LLC

Janak Jadeja, R.Ph.
Director, Regulatory Affairs

Actavis Elizabeth LLC | 200 Elmora Avenue | United States | t (908) 527 9100 | @ actavis@actavis.com
Actavis Mid-Atlantic LLC | Elizabeth, NJ 07207 | f (908) 659 2250 | w www.actavis.com

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 3

FROM: Liang-Lii Huang

DATE: Nov 18, 2008

ANDA: 78-223

NAME/TITLE OF INDIVIDUAL(S) from FDA: Liang-Lii Huang, review chemist

FIRM: Actavis Mid Atlantic LLC Representative: Chris Shearn
PRODUCT NAME: Clobetasol Propionate Lotion, 0.05%
TEL #: (908) 659-2619

Notes of Conversation:

Deficiency:

Please commit to placing the drug samples packaged using a new cap manufacturer, (b) (4) for the 2 oz and 4 oz container/closure system for stability studies in your annual update.

SIGNATURE OF OGD REPRESENTATIVES:
Liang-Lii Huang, Ph.D., review chemist

Location of Electronic Copy:

V:\Chemistry Division I\Team 3\T-CONS\78223.TCON.doc

November 18, 2008

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

/s/

Liang Lii Huang
11/25/2008 11:25:20 AM
CHEMIST

James Fan
11/25/2008 12:54:22 PM
CHEMIST

Rosalyn Adigun
11/25/2008 01:41:07 PM
CSO